CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-896/S-006

MEDICAL/STATISTICAL REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-860/150 A. Rahman / Sophia Abraham, PhD			FROM: HFD-150: A. Martin, M.D./ M. Pelosi, CSO	
4-10-01	IND NO.	NDA NO.20-896 SE1-006	TYPE OF DOCUMENT: Population PK Analysis	DATE OF DOCUMENT 10-23-00
NAME OF DRUG Xeloda)	PRIORITY CONSIDERATION: P		CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: April 16, 2001

NAME OF FIRM: Roche

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE–NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

SOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES
☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The Clin Pharm reviewer for Xeloda did not comment on the "Evaluation of Age & Creatinine Clearance as Covariates in Population PK Analysis of Capecitabine and its Metabolites." Therefore the MO has had to review this information herself and would like the Clin Pharm reviewer toamend her original review (or do a short second review) to address the issues and verify that the MO's interpretation of the analysis is accurate..

SIGNATURE OF REQUESTER: M. Pelosi for A. Martin, MD	METHOD OF DELIVERY : HAND - X
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER: M. Pelosi 4-10-01

CC: NDA 20-896/SE1-006
HFD-150/Div File
/ **Pelosi**, Rahman, Abraham, Martin

Evaluation of Age and Creatinine Clearance as Covariates in Population Pharmacokinetic Analysis of Capecitabine and its Metabolites

FOR

XELODA® (Capecitabine)

ctober 23, 2000

NDA 20-896
Xeloda® (capecitabine, Ro09-1978) Tablets
Supplement - Changes Being Effected (Labeling Revisions)

October 23, 2000

VOLUME 2
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Biople Sect 4 vol 2 by [illegible].

BEST POSSIBLE COPY

√ Table 4, p 10 — related vs unrelated

√ premature w/D — ? dose reduction in moderate?

√ [illegible] related death, p 11

p 10 - 'all serious [illegible]' [illegible] related vs p16

Rationale p22
mild - [illegible] - [illegible]

A. Population PK Data from the Two Randomized Phase 3 Colorectal Studies

Population PK analyses were performed as part of a prospectively designed protocol primarily for the phase 3 colorectal trials. Data was pooled from sparsely sampled plasma from 482 patients enrolled on the two phase 3 colorectal cancer trials as well as 24 patients from a bioequivalence study of a single dose of xeloda. The NONMEM modeling program tested the impact of the following covariates: gender, age, race, performance status, body surface area, creatinine clearance, hepatic transaminases, total bilirubin alkaline phosphatase, presence or absence of liver metastases at baseline, serum albumin and trial.

The results were submitted with the colorectal sNDA and have previously been reviewed by Clinical Pharmacology/Biopharmaceutics. The modeling indicated that there was a statistically significant association of age with the AUC of FBAL. However, a multivariate model indicated that this was due to an association between age and creatinine clearance.

Additional NONMEM analyses that assess the relative importance of age and creatinine clearance are submitted as part of this amendment. Analyses of the effect of age on clearance and volume of FBAL alone and together. The objective function remained stable or dropped. The objective function increased, however, after removing the effect of creatinine clearance on both clearance and volume of FBAL.

Conclusion: Sponsor and FDA reviewers agree that the effect of creatinine clearance is stronger than the effect of age, as concluded in the review of the sNDA filing.

APPEARS THIS WAY
ON ORIGINAL

MEDICAL OFFICER REVIEW OF AN AMENDMENT
SE1-006 SUBMITTED TO N20-896
(Response to an Approvable Letter)

NDA: 20-896

Serial Number: SE1 - 006

Drug Name: Xeloda® (capecitabine) Tablets

Sponsor: Hoffmann-LaRoche Inc.

Type of Submission: Amendment: Response to the FDA's AE Letter dated 9/20/00

Submission Date: October 31, 2000

PDUFA Due Date: April 30, 2001

Indication: First-line treatment of metastatic colorectal cancer

Consultations: Clinical Pharmacology/Biopharmaceutics
Biometrics

This review addresses Hoffman-La Roche's response to an approvable letter issued September 20, 2000 for use of Xeloda as first-line treatment of metastatic colorectal cancer. The sponsor's submission consists of the following:

- Volume 1: revised labeling and overview of the submission.
- Volumes 2-8:
  (a) final study report for WP15811 (clinical pharmacology study conducted in patients with renal impairment);
  (b) safety analyses of the overall clinical trial database (875 patients);
  (c) additional population PK analyses based on data from the two phase 3 colorectal trials assessing the covariates of age and creatinine clearance.
- Disk containing corresponding PK datasets for WP15811.
- A second disk was requested and submitted, allowing confirmation of statistical analyses performed on the overall clinical trial database.

BACKGROUND

Original Approval. The original NDA for Xeloda (capecitabine) received accelerated approval under Subpart H of 21 CFR 314.500 in 1998 for a population of patients with breast cancer. The indication reads: "treatment of patients with breast cancer resistant to

both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents."

sNDA in Colorectal Cancer (SE1-006). The sNDA was submitted September 20, 1999 for the first-line treatment of patients with metastatic colorectal cancer. An "approvable" letter issued September 20, 2000. The following deficiencies and phase 4 commitments are excerpted from the letter.

1. "Provide the final study report, individual patient data, and statistical analysis for the completed study, WP15811 (Effect of Renal Impairment on the Pharmacokinetics of Capecitabine in Cancer Patients). We note that your September 13 and 14, 2000 amendments stated that your preliminary assessment is that contraindications and dose modifications will be necessary in some groups of patients with renal impairment. Please finalize and submit these recommendations to the NDA, accompanied by data sufficient to allow the Agency to confirm the advice.

2. Submit draft printed labeling revised as follows:

   - Please incorporate renal impairment information from study WP15811, including contraindications and dose modifications.

   - Please incorporate information supporting the conclusion of non-inferiority in survival. Point estimates may be included but are not by themselves sufficient to conclude non-inferiority.

   - Please accept our latest draft marked-up changes or propose revisions. We reserve the right to make additional revisions, as needed, after your resubmission.

In addition, the following Phase 4 commitments were required prior to approval:

- Update the survival analyses after a total of 1180 deaths have occurred in the two randomized controlled trials, SO14694 and S)14796. Please provide a timeframe for this data to be submitted.

- Submit results of the _____ and _____ clinical trials in advanced metastatic colorectal cancer studying Xeloda in combination with irinotecan when completed. If other trials are initiated with this combination, please submit the results when available."

REVIEW OF SUBMISSION

I. Final Study Report for WP15811: Effect of Renal Impairment on the PK of Capecitabine in Cancer Patients – See Clinical Pharmacology/Biopharmaceutics Review

Please see the Clinical Pharmacology/Biopharmaceutics Review for details of the study design and PK results. To summarize, 27 cancer patients were enrolled in an open-label, parallel design, steady-state phase 1 trial. The four degrees of renal impairment included in the study correlate with the categories recommended in the 1998 CDER/CBER Guidance for Industry.

Both sponsor and FDA agree that PK analysis identifies a major increase in the systemic exposure to FBAL, the metabolite with a 50% rate of excretion in the urine. In patients with moderate and severe renal impairment, systemic exposure to FBAL on day 1 ($AUC_{0-\infty}$) was 85% and 258% increased over normal, respectively. On day 14, the increase was 69% and 315% over normal for moderate and severe renal impairment, respectively. An increase was not seen in patients with mild renal impairment. This result is consistent with a meta-analysis of PK data from 4 phase 1 studies and with the population PK analyses on the two randomized phase 3 trials in colorectal cancer (submitted with the sNDA and previously reviewed).

An increase in systemic exposure to the immediate precursor to 5-FU, 5'-DFUR, was seen on day 1 (42% and 71% for moderate and severe impairment, respectively); however, the increase was less apparent and not statistically significant on day 14 (29% and 16%, respectively). There was no evidence for a consistent effect on capecitabine, 5-FU or 5'-DFCR with any degree of renal failure.

Reviewer Note: The sponsor's logistic regression curves plotting the probability of treatment-related grade 3-4 adverse events vs. AUC of FBAL, 5'-DFUR and 5-FU on day 14 suggest that the AUC of 5-DFUR correlates most closely with clinical toxicity. However, FBAL is the metabolite demonstrating the greatest increase in AUC when creatinine clearance decreases.

Reviewer Table 1 presents the clinical safety data by degree of renal impairment.

Reviewer Table 1: Number of Patients with Adverse Event by Degree of Renal Impairment*

	Normal 6		Mild 8		Moderate 9		Severe 4	
Median treatment duration in days (range)	114 (14 – 209)		159 (14 – 426)		74 (14 – 138)		35 (13 – 79)	
All adverse events	6	(100%)	8	(100%)	9	(100%)	4	(100%)
Number of pts with Gr 3 toxicity	6	(100%)	7	(88%)	8	(88%)	4	(100%)
Number of pts with Gr 4 toxicity	-	-	-	-	1	(11%)	2	(50%)
Number of pts with serious adverse events	3	(50%)	5	(62%)	8	(100%)	4	(100%)
Withdrawals due to toxicity	1	(17%)	2	(25%)	1	(11%)	4	(100%)
Deaths on study or within 28 days	-	-	1 - PD	(12%)	1 - PE	(11%)	1 – PD 1 – ARF, Sepsis	(25%)
Response Rate	0	(0%)	1	(12%)	1	(11%)	0	(0%)

* Data derived from Clinical Pharmacology/Biopharmaceutics review and sponsor's Tables 28, 29, 31, 38 in v. 3.
PD = progressive disease; PE = pulmonary embolism; ARF = acute renal failure

Four patients died within 28 days of study drug. Three were considered to be unrelated to treatment by the investigator; however, the death of one patient with severe renal impairment was considered "probably" related to treatment. Patient #22847/0044 was a 70 year old female with metastatic colon cancer and a creatinine clearance of 28 ml/min. Study drug was stopped on day 13 due to toxicity. On day 20, the patient had neutropenia, diarrhea and worsening renal failure (creatinine clearance of 15 ml/min), culminating in death on day 25, despite supportive care.

Reviewer Note: Although bowel perforation could be related to underlying disease, Xeloda has been associated with necrotizing colitis which produces a similar clinical picture. The temporal relationship to drug administration and presence of concurrent known drug-toxicities supports the diagnosis of a drug-related death.

II. Analyses of the Overall Clinical Safety Database (#875) by Baseline Creatinine Clearance

The overall clinical safety database supporting the claims of the sNDA consisted of 875 patients: 630 received xeloda in colorectal cancer trials (596 from the two phase 3 trials SO14695 and SO14796; 34 from a phase 2 study) and 245 received xeloda in phase 2 breast cancer trials. The sponsor submits analyses of safety parameters by degree of renal impairment (retrospectively determined in the majority of patients by a calculated baseline creatinine clearance according to the Cockroft and Gault formula). Information on baseline creatinine clearance was available for 861 patients.

Reviewer Table 2: Overall Clinical Safety Database by Baseline Creatinine Clearance

	Xeloda			
	Creatinine Clearance (ml/min)			
	Normal >80	Mild 51-80	Moderate 30-50	Severe <30
# Pts	398	373	84	6
Median Age	56	66	74	75
Median Duration of Rx (days)	131.5	127	114.5	48
# Pts with Gr 3/4 toxicity (Rx-related)	141 (33%)	155 (42%)	46 (55%)	2 (33%)
# Pts with Gr 4 toxicity (Rx-related)	6 (2%)	15 (4%)	6 (7%)	2 (33%)
# Pts with SAE (Rx-related)	38 (10%)	56 (16%)	14 (17%)	3 (50%)
# Pts withdrawn (Rx-related)	29 (7%)	47 (13%)	15 (18%)	1 (17%)
# Rx-related Deaths	1 (0.3%)	6 (1.6%)	2 (2.4%)	1 (17%)
# Pts with Gr 3/4 toxicity (all)	210 (53%)	217 (58%)	55 (65%)	2 (33%)
# Pts with Gr 4 toxicity (all)	30 (8%)	42 (11%)	10 (12%)	2 (33%)
# Pts with SAE (all)	125 (31%)	136 (36%)	34 (40%)	3 (50%)
# Pts withdrawn (all)	47 (12%)	65 (17%)	17 (20%)	1 (17%)
# All Deaths on drug or w/in 28 days	35 (9%)	37 (10%)	9 (11%)	1 (17%)
Response Rate	25%	27%	24%	40%

Based on data from v. 45.2 and data forwarded from HLR on April 11, 2001.

Reviewer Comment: Analysis of the overall safety database is limited by a single calculated baseline creatinine clearance. Nevertheless, it appears that toxicity measured by a number of parameters may increase with decreasing creatinine clearance. Patients categorized as having severe renal failure do not reach the level of severe toxicity seen in the clinical pharmacology trial, but the length on treatment is short compared to patients with other degrees of renal function.

III. Comparative Analyses of Safety from the Two Phase 3 Studies (SO14695 and SO14796) in Patients with Renal Impairment at Baseline

Reviewer Table 3 presents parameters of moderate to severe toxicity by degree of renal impairment in the two controlled studies in colorectal cancer. Renal function was retrospectively determined by a calculated creatinine clearance (Cockroft and Gault formula). Again, the analyses are limited by a using only a single calculated baseline creatinine clearance for correlations over time.

Reviewer Table 3: Comparative Analyses of Safety from SO14695 and SO14796

	Xeloda				5-FU/LV			
	Creatinine Clearance (ml/min)				Creatinine Clearance (ml/min)			
	Normal >80	Mild 51-80	Moderate 30-50	Severe <30	Normal >80	Mild 51-80	Moderate 30-50	Severe <30
# Pts	268	257	59	5	261	265	61	0
Median Age	58	67	74	79	58	66	73	-
Median Duration of Rx	147	139	126	48	117	130	89	-
# Pts with Gr 3/4 toxicity (Rx-related)	96 (35.8%)	104 (40.5%)	32 (54.2%)	2 (40%)	81 (31.0%)	93 (35.1%)	31 (50.8%)	-
# Pts with Gr 4 toxicity (Rx-related)	1%	3%	7%	40%	4%	5%	10%	-
# Pts with SAE (Rx-related)	26 (10%)	41 (16%)	10 (17%)	3 (60%)	43 (16%)	55 (21%)	23 (38%)	-
# Pts withdrawn (Rx-related)	15 (6%)	30 (12%)	10 (17%)	1 (20%)	14 (5%)	18 (7%)	8 (13%)	-
# Pts with Gr 3/4 toxicity (all)	138 (51%)	146 (57%)	41 (69%)	2 (40%)	117 (45%)	125 (47%)	37 (61%)	-
# Pts with Gr 4 toxicity (all)	16 (6%)	29 (11%)	6 (10%)	2 (40%)	22 (8%)	23 (9%)	8 (13%)	-
# Pts with SAE (all)	29%	38%	42%	60%	32%	38%	54%	-
# Pts withdrawn (all)	10%	21%	25%	20%	11%	14%	30%	-
Response Rate	25%	27%	24%	40%	16%	19%	10%	-

Composite of sponsor's table 7 from v. 45.2 and

The sponsor and the medical reviewer agree on the following conclusions:

1. A trend for an increased incidence of treatment-related grade 3 and 4 adverse events, serious events and number of patients withdrawn due to toxicity is seen in patients with moderate and severe renal failure (limited to severe renal failure in WP15811).
2. The incidence of toxicity with xeloda appears similar to that of the alternative treatment, 5-FU/LV.
3. The response rate appears stable despite degrees of renal impairment, including in patients with severe renal impairment. There were no tumor responses in the four patients with severe renal impairment in WP15811.

Sponsor and the reviewer have the following disagreements in conclusions:

1. The sponsor states that "5-FU/LV treatment benefits are less pronounced than with xeloda." An assessment of risk:benefit ratio should factor survival, not response rate, as the benefit of interest. The endpoint that could support approval for first-line treatment of colorectal cancer is survival. The statistically significant difference in response rates favoring xeloda did not translate into superiority in survival.

2. The sponsor provides data demonstrating fewer dose reductions and a longer median time to dose reduction for patients receiving xeloda compared to those receiving 5-FU/LV. These arguments are not persuasive, as originally discussed in Section 11.2 of the joint medical/statistical review of the sNDA. Briefly, criteria for dose modifications differed between the arms, e.g., for a grade 2 toxicity, treatment with Xeloda would be temporarily interrupted with resumption of a normal dose. For grade 2 toxicity with 5-FU/LV, a 20% reduction in dose was prescribed. Furthermore, the relevance of dose modifications is unclear since patients on xeloda received a mean of 84% of the planned dose and patients on 5-FU/LV received a mean of 89% of the planned dose.

IV. Age and Creatinine Clearance

A. Safety Profile by Age

The sponsor provides an analyses of safety for the 875 patients in the clinical trial database by age. Reviewer Table 4 collapses the categories into decades; sponsor table 8, volume 45.2, presents the data by five year intervals between50 and 80.

Reviewer Table 4: Safety Profile by Age

	<50	50 – 59	60 – 69	70 – 79	> 80
# Pts	133	225	286	210	21
# Pts with gr 3 or 4 rx-related events	39 (29%)	86 (38%)	116 (41%)	96 (46%)	13 (62%)
# Pts with serious rx-related events	14 (11%)	20 (9%)	40 (14%)	36 (17%)	7 (33%)
# Pts withdrawn due to any AE, lab abnormality of death	17 (13%)	19 (8%)	45 (16%)	49 (23%)	8 (38%)

Based on data from Sponsor Table 8, volume 45.2

The trend in number of patients with grade 3 or 4 treatment-related events, serious treatment-related adverse events and patients withdrawn due to any adverse event, lab abnormality or death increases with age. No statistical comparisons are made.

B. Univariate and Multivariate Cox Regression Analyses – see Biometrics Review

The sponsor performed multivariate Cox regression analyses on time to first occurrence of related key adverse events, specifically diarrhea, stomatitis, nausea, vomiting, hand-foot syndrome and neutropenia. Of the 10 covariates tested, age, race (black vs. other) and baseline creatinine clearance were selected into the multivariate analysis. The sponsor states that age and creatinine clearance have a similar impact on the occurrence of the key adverse events in univariate analyses; however, age did not have an additional significant impact in the multivariate analysis.

The sponsor used a continuous variable for age. The FDA analysis tested the impact of age < 60 or ≥ 60 and age < 80 and ≥ 80. When age is assessed by a cutoff of 60 years, no significant impact is seen after adjusting for creatinine clearance (p = 0.64). When age is assessed by a cutoff of 80 years, the p value is 0.06. Patients 80 years of age or older may have an 80% higher risk of toxicity than those younger than 80, after adjusting for creatinine clearance. Analysis is limited by the small number of patients (n = 21).

Additional analyses by FDA Biometrics indicate that time to adverse events using two rather than four categories of renal impairment (≤ 50 and > 50), indicates increased risk limited to the group of patients with ≤ 50 cc/minute. This lends additional support to the sponsor's conclusion that dose modifications are not needed in patients with mild renal impairment.

Reviewer Comment: It should be noted that the Cox regression analyses were conducted with time to **related** *events. No analyses are presented based on time to* **all** *adverse events or on data from the control arm of 5-FU/LV for comparison.*

The meaning of defining race as "Black" or "other" in these analyses is unclear. Furthermore, the number of black patients is small – 28. A formal pharmacology study of japanese vs. caucasian patients is being conducted under Japanese IND. Consideration could be given to requesting that this data be submitted to the US IND if the impact of race is to be further explored.

The current label includes a warning for geriatric patients, specifically patients 80 years of age or older. However, the warning limits itself to an excess of gastrointestinal toxicities, minimizing that the overall incidence of grade 3 and 4 toxicity is 62% in the two phase 3 trials.

C. Population PK Data from the Two Randomized Phase 3 Colorectal Studies – See Clinical Pharmacology/Biopharmaceutics Review

Population PK analyses were performed as part of a prospectively designed protocol primarily for the phase 3 colorectal trials. Data was pooled from sparsely sampled plasma from 482 patients enrolled on the two phase 3 colorectal cancer trials as well as 24 patients from a bioequivalence study of a single dose of xeloda. The NONMEM modeling program tested the impact of the following covariates: gender, age, race, performance status, body surface area, creatinine clearance, hepatic transaminases, total bilirubin alkaline phosphatase, presence or absence of liver metastases at baseline, serum albumin and trial.

The results were submitted with the colorectal sNDA and have previously been reviewed by Clinical Pharmacology/Biopharmaceutics. Age was not a significant factor affecting the pharmacokinetic parameters of 5'-DFUR, 5-FU and FBAL in the population pharmacokinetic model. However, a separate regression analysis of the same data showed that a 20% increase in age is associated with a 15% increase in FBAL AUC.

Additional NONMEM analyses addressing the relative importance of age and creatinine clearance are submitted as part of this amendment. Those analyses assessing the effect of age on clearance and volume of FBAL (alone and together) did not change the objective function of the model. The objective function increased, however, after the covariate of creatinine clearance was replaced by age, indicating significance of creatinine clearance on FBAL clearance and volume of distribution.

Conclusion: Sponsor and FDA reviewers agree that the population PK data suggest that the effect of creatinine clearance is stronger than the effect of age. This is consistent with conclusions in the initial review of the colorectal sNDA.

V. Summary and Recommendations for Dose Modifications for Renal Impairment

The sponsor submitted the following recommendations for dose modification for renal impairment. These recommendations were previously distributed to practitioners in a Dear Health Care Practitioner letter in November, 2000.

- Xeloda is contraindicated in patients with severe renal impairment (calculated CrCl < 30 mL/min by Cockroft and Gault).
- In patients with moderate renal impairment (creatinine clearance 30-50 mL/min at baseline, a dose reduction to 75% of the Xeloda starting dose is recommended.
- In patients with mild renal impairment (creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event with subsequent dose adjustments as outlined in the table in DOSAGE AND ADMINISTRATION.

Reviewer Comment: These proposals for dose modification are acceptable to the medical and clinical pharmacology/biopharmaceutics reviewers.

PHASE 4 COMMITMENTS

The sponsor agrees to the two Phase 4 commitments: (a) submission of a survival update for the two randomized controlled trials, SO14696 and SO14796, after 1180 deaths (target submission December 2002; and (b) submission of the results of clinical trials adding irinotecan to Xeloda.

RECOMMENDATION

Approval of the sNDA. Dose modifications for renal impairment are acceptable based on the data submitted. Agreements need to be reached with regard to final labeling. Consideration should be given to two additional phase 4 commitments:

- Please submit the final study report for #BP15831, "Comparison of the pharmacokinetics of capecitabine in Japanese and Caucasian cancer patients." We note that a retrospective analysis (report #B-164833) performed on pooled data from seven phase l studies suggested differences between these two populations.

- Please identify and submit final study reports for all trials assessing the activity (phase 2) or efficacy (phase 3) of capecitabine as second-line therapy in patients with colorectal cancer previously treated with a fluoropyrimidine-based therapy.

/S/ 4/26/07
Alison Martin, M.D.

APPEARS THIS WAY
ON ORIGINAL

sNDA # 20-896: Xeloda™ (capecitabine)

Applicant: Hoffmann-La Roche Inc.

Indication:

First-line treatment of metastatic colorectal cancer

FDA MEDICAL and STATISTICAL REVIEW

Medical Reviewer:	Alison Martin, M.D.
Statistical Reviewers:	Ning Li, M.D., Ph.D.
	Mark Rothmann, Ph.D

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1. General Information

1.1 Name of Drug

Established: Capecitabine (Ro 09-1978)
Proprietary: Xeloda™
Chemical: N^4-Pentyloxycarbonyl-5'-doxy-5-fluorocytidine

1.2 Applicant

Hoffman La-Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

1.3 Pharmacologic Category

Antineoplastic; 5-fluorouracil pro-drug; fluoropyrimidine carbamate

1.4 Proposed Indication

"Xeloda is indicated as first-line treatment of patients with metastatic colorectal carcinoma."

1.5 Dosage and Administration

No changes are proposed to the current package insert, which reads:

"The recommended dose of Xeloda is 2500 mg/m^2 administered orally daily with food for 2 weeks followed by a 1-week rest period given as 3-week cycles. The Xeloda daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. Xeloda tablets should be swallowed with water."

1.6 How Supplied

Xeloda is supplied as biconvex, oblong film-coated tablets, available in two dose strengths, 150 and 500 mg.

2. Regulatory History

The initial IND for capecitabine was filed May 20, 1994. On April 30, 1998, Xeloda received accelerated approval on the basis of a single phase 2 trial for "the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents." Two phase 4 commitments are pending.

The EOP-2 meeting for an indication in colorectal cancer was held September 9, 1996. Agreement was reached with regard to patient population, control arm and need for two studies. The sponsor was planning two protocols, one which would enter patients primarily from the U.S. and a second predominantly European protocol, each for simultaneous multinational registration and mutual support. The EU had accepted RR as a primary endpoint; the sponsor had a priority of keeping the two protocols identical to allow pooling of the data. The FDA stated that survival was the primary endpoint of interest for this population in the U.S. and that RR would not stand alone. As a compromise position, TTP was agreed to as a co-primary endpoint (although the protocol was not modified for multiple endpoints). The FDA further stated that negative trends in TTP and survival would override any perceived benefit in RR. Therefore this application suffers from a discrepancy between the protocol-specified endpoint and the primary endpoint of interest to the Agency.

3. **Scope of Review**

The medical review of sNDA #20-896 included:

- Regulatory history of the application
- Original submission of protocols SO14795 and SO14796, with amendments
- The following volumes of the NDA submission: index (vol. 1), labeling (vol. 2), summary (vol. 3), clinical data section 8/10 (vol. 30 - 180) and the Safety Update report submitted January 21, 2000 consisting of 7 volumes
- Pertinent MS Access database files and electronic case report forms and tabulations
- Consult to HFD-430 for evaluation of post-marketing safety surveillance
- Last annual report submitted to IND [redacted] correspondence date of August 27, 1999.

The statistical review of the NDA included:

- The following volumes of the NDA submission: vol. 1-4, 30-38, 50-79
- SAS files and programming code
- Bayesian analysis of survival submitted March 15, 2000.

4. **Chemistry and Manufacturing (see Chemistry Review)**

5. **Clinical Pharmacology/Pharmacokinetics (see Clinical Biopharmaceutical Review)**

- **Carcinogenicity data**. The submitted mouse study is considered by the consultant, reviewer and Executive CAC to have used doses too low to be informative (one-tenth the recommended human dose). Furthermore, capecitabine is metabolized to a mutagenic carcinogen, 5-FU, which was not generated in some of the test systems. Although this indication does not require conclusive carcinogenicity data, claims in the label will need to be changed.

The following summary points are reviewed in detail in the Clinical Biopharmaceutical review. Only new information since accelerated approval is mentioned.

- **Population PK.** Population PK analyses were performed on pooled, sparsely sampled plasma data from 482 patients from the two phase 3 colorectal cancer trials and 24 from a bioequivalence study of a single dose. The NONMEM modeling program was used to assess the influence of clinical covariates on the PK of capecitabine and metabolites (parent compound is inactive). Results indicated that gender, age, race, PS, hepatic transaminases, presence or absence of liver metastases at baseline and serum albumin were not important covariates in the model. Alkaline phosphatase and body surface area were considered significant (see below).

- **Age.** Population PK analysis on a total of 505 patients from the phase 3 trials did not indicate that age was an important covariate in the model. However, a univariate analysis demonstrated a statistically significant association with age and AUC of FBAL, which is considered to result from the positive correlation of creatinine clearance to clearance of FBAL. (For clinical data, see section 10, Integrated Summary of Safety)

- **Gender.** The prior (accelerated) approval of capecitabine was based on data from women (breast cancer indication). The efficacy claims for this sNDA are based on 1207 patients, 60% of whom are male. Population PK analysis on a total of 481 patients from the two phase 3 trials did not indicate that gender was an important covariates in the model.

- **Renal Impairment.** The population PK analyses performed on the two randomized trials resulted in statistically significant results for creatinine clearance on clearance and volume of FBAL, a capecitabine metabolite, but did not affect the PK of 5'-DFUR or 5-FU. Since FBAL is not considered to be responsible for efficacy, the findings were of uncertain significance. A recently completed phase 1 study in patients with renal impairment (WP15811) reported one death on study. The Agency is awaiting submission of the full study report.

- **Hepatic Impairment.** Data submitted to the original NDA from BK14822: Influence of hepatic impairment due to liver metastases on the PK of capecitabine in cancer patients indicated that Cmax of 5-FU was increased by 28% and AUC of 5-FU was increased by 15% in patients with mild to moderate hepatic dysfunction after a single dose of study drug.

  The population PK analyses performed on the two randomized trials showed statistically significant results for the influence of alkaline phosphatase on clearance of 5-FU and the metabolite FBAL. This effect was not reproduced with other potential measures of hepatic function, e.g. transaminases, total bilirubin, and presence or absence of liver metastases at baseline. The clinical significance of this finding is uncertain.

- **Ethnicity.** There wasn't a statistically significant effect on PK per population PK analyses, which included 505 patients: 455 Caucasian, 22 Black and 28 with race categorized as "other". Due to the small sample size of noncaucasians, no definitive conclusions can be drawn.

- **Drug-Drug Interactions.**

  Warfarin. A potential drug interaction between capecitabine and warfarin was detected during post-marketing surveillance by both the Agency and the sponsor (ref. OPDRA consult dated March 26, 1999 and Dear Health Professional Letter dated March 1999). Protocol ____ entitled "Effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin," is ongoing. The mechanism of the interaction is not yet known but frequent monitoring of coagulation parameters is advised in the label.

  Phenytoin. A potential interaction between capecitabine and phenytoin was detected by review of 15-day adverse event reports. The sponsor has submitted a labeling supplement to ask for frequent monitoring of phenytoin levels. Comments on the supplement will be included with the labeling review of this application.

  Leucovorin. The phase 1 trial SO14798 evaluated the effect of leucovorin (30 mg b.i.d.orally) on the PK of capecitabine (829 and 1000 mg/m^2 b.i.d). The PK of capecitabine and its metabolites were not effected except for 5-FU, whose mean AUC and Cmax increased by 90% and 55%, respectively, when leucovorin was coadministered with capecitabine 1000 mg/m^2 b.i.d. Conversely, capecitabine at the phase 3 dose decreased the AUC and Cmax of leucovorin (30 mg) by 45% and 30%, respectively.

- **Concentration-Effect Analyses.** Regression analyses of correlations between AUC and Cmax of capecitabine metabolites from the 481 colorectal cancer patients from the two phase 3 trials were performed. Overlap in systemic exposures between patients with and without objective tumor responses and with and without grade 3 and 4 adverse events precluded dosing recommendations based on pharmacokinetics.

6. Related IND Submissions

See Appendix I: Summary of Clinical Trials with Capecitabine

7. **Pivotal Trial: Protocol SO14695: An open-label randomized phase III study comparing capecitabine with 5-fluorouracel in combination with leucovorin as first-line chemotherapy in patients with advanced and/or metastatic colorectal carcinoma**

7.1 Protocol Review

Principal Investigator: Dr. Richard Pazdur
M.D. Anderson Cancer Center
Houston, Texas, USA

Reviewer Table 1: Protocol SO14695 Milestones

Milestone	Date	# Pts Entered	Highlights/Comments
First Patient Randomized	October 2, 1996		
Amendment 1	July 7, 1997	254	Redefinition of PD from 25 to 50% ↑. Added details of a Cox regression analysis.
Amendment 2	November 10, 1998	605	Changes to statistical analysis plan. Clarified ITT analysis = all randomized pts. Added longitudinal analysis. Clarified noninferiority test for TTP or death.
Last Patient Randomized	October 10, 1997		
Original or "Clinical" Data Cutoff	Cutoff: September 24, 1998		Min f/u 7 mo. # events: 53.5-56.3%
First Survival Update (Submitted w/ NDA*)	Cutoff: January 24, 1999		Min f/u 11 mo. # events: 62-64.5%
NDA Submission	September 20, 1999		
Second Survival Update (Submitted w/ Safety Update)	Cutoff: September 15, 1999		# events: 79-80%
Third Survival Update (Requested by FDA)	Cutoff: May 15, 2000		# events: 86-90%

*Submitted with NDA; two additional survival analyses were presented in preNDA meetings.

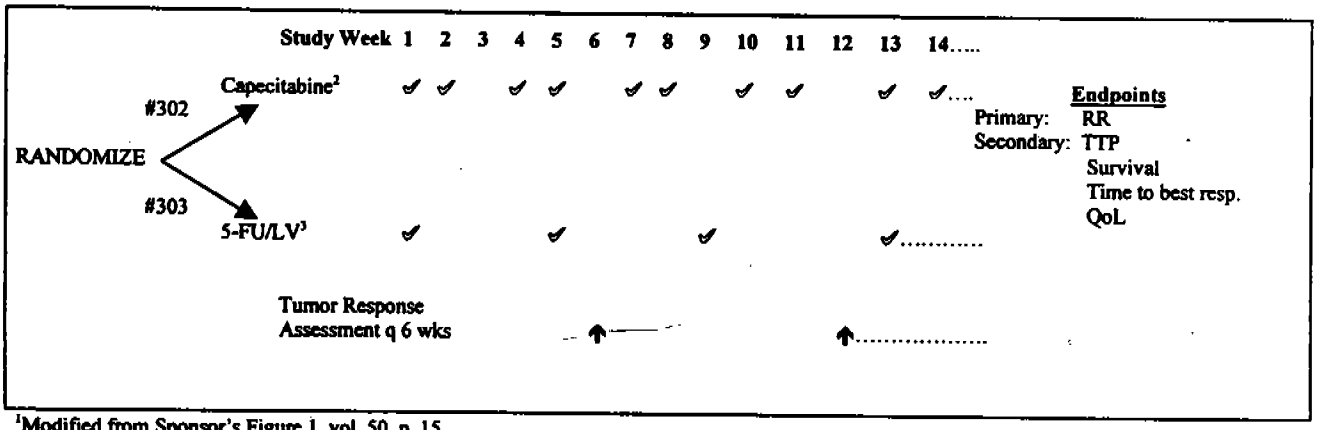
Reviewer Comment: *Shading identifies replacement text from the amendment in the review below. The original text is identified by a ~~strikethrough~~. The two amendments were primarily clarifications. The exception is redefinition of PD after a significant number of patients were entered. However, the endpoints of response rate and TTP were subject to "reconciliation" by the sponsor (see Section 7.2.3.1 of the review) so that one interpretation of PD prevailed and was consistent for the entire study, albeit retrospectively.*

7.1.1 Synopsis

Protocol SO14695 was a multicenter (61 sites), international (4 countries), controlled, randomized phase 3 trial in patients receiving first-line chemotherapy for metastatic colorectal cancer. The protocol-defined primary endpoint was demonstration of equivalency in response rate (CR + PR) between capecitabine 1250 mg/m2 BID daily for 14 days followed by a one week rest (3 week cycle) and the control arm, the Mayo Clinic regimen of 5-FU + LV (20 mg/m^2 LV IVB followed by 425 mg/m^2 5-FU IVB on days 1-5 q 28-day cycle). Secondary endpoints included time to progression (TTP), survival, time to best response and QoL as measured by the EORTC QLQ-C30 questionnaire.

Randomization was assigned by country, using a block size of 6. The U.S. was further stratified by 4 regions. Responses were assessed every 6 weeks until week 30. At this point, patients with CR, PR and ~~SD~~ could continue treatment on the "continuation phase" until week 48. Patients with CR, PR and SD could continue treatment beyond week 48 on the "post-continuation phase." After a patient went off study drug, follow up was to occur every 3 months.

Figure 1 Schema



[1]Modified from Sponsor's Figure 1, vol. 50, p. 15
[2]Capecitabine treatment: 14 days of 1250 mg/m^2 BID followed by 7 day rest (3 week cycle)
[3]5-FU/LV treatment: 20 mg/m^2 LV IVB followed by 425 mg/m^2 5-FU IVB on days 1-5 q 28-day cycle

7.1.2 Objectives

Primary:

- To demonstrate at least equivalency in RR (CR + PR) of capecitabine to 5-FU/LV

Secondary:

- To compare TTP, survival, time to best response, duration of response
- To compare safety profiles
- To evaluate and compare changes in QoL
- To evaluate and compare medical care utilization
- To explore intra- and interpatient variability in PK and identify factors that influence it (e.g. BW, creatinine clearance)
- To explore the relationship between efficacy/toxicity parameters and systemic exposure (AUC)

7.1.3 Eligibility Criteria

- Histologically or cytologically confirmed colorectal adenocarcinoma with advanced and/or metastatic disease
- At least one bidimensionally measurable lesion according to WHO criteria
- Minimum indicator lesion size as follows:
  --liver, soft tissue and masses (CT scan): at least one diameter $\geq$ 20 mm
  --lung (CXR, CT scan) with at least one diameter $\geq$ 10 mm
  --skin lesions, nodes: at least one diameter $\geq$ 10 mm
- 18 years or older
- KPS $\geq$ 70%
- Life expectancy $\geq$ 3 months
- Written informed consent

7.1.4 Exclusion Criteria

- Pregnant or lactating women; positive or no pregnancy test at baseline. Reliable contraception for males and females

- Prior cytotoxic chemotherapy except if given as adjuvant or neoadjuvant treatment and completed at least 6 months before treatment start
- Clinically significant cardiac disease (e.g. CHF, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication) or MI within the last 12 months
- CNS metastases; patients with a history of uncontrolled seizures, CNS disorder, psychiatric disability judged by the investigator to be clinically significant precluding IC or interfering with compliance for oral drug intake
- History of another malignancy [redacted] except cured basal cell carcinoma of skin and carcinoma in-situ of the uterine cervix
- Following abnormal laboratory values:
  --ANC $\leq$ 1.5 x 10^9/l, platelet count < 100 x 10^9/l
  --S. creatinine or s. bilirubin $\geq$ 1.5 x upper normal limit
  --hepatic transaminases > 2.5 x upper normal limit or > 5 x upper normal limit in the case of liver metastases
  --alkaline phosphatase > 2.5 x upper normal limit or > 5 x upper normal limit in the case of liver metastases of > 10 x upper normal limit in the case of bone disease
- XRT within 4 weeks of treatment start
- Major surgery within 4 weeks and have not fully recovered
- Any investigational drug study within 4 weeks of treatment
- Serious, uncontrolled infections
- Lack of physical integrity of UGI tract or malabsorption

7.1.5 Treatment

Capecitabine is administered orally at a total daily dose of 2500 mg/m^2 to be taken in two doses approximately 12 hours apart, e.g. breakfast and dinner. The dose should be taken within 30 minutes after the end of a meal and swallowed with approximately 200 ml of water (not fruit juice). Capecitabine is given daily for 14 days, followed by a one week rest.

Leucovorin 20 mg/m^2 is given as a rapid IV injection followed by an IV bolus of 425 mg/m^2 5-FU, daily from day 1 to 5 every 28 days.

7.1.6 Concomitant Medication and Treatment

Concomitant medication and treatment were to be recorded on the CRF. There were no prohibitions; however, imodium was recommended for diarrhea and H_2-receptor antagonists over antacids. Radiotherapy to a bone lesion for pain was allowed if at least one indicator lesions remained outside the field.

Reviewer Comment: *The sponsor was asked on 6/20/00 to summarize any anticancer treatment given to a patient while on study.*

7.1.7 Schedule of Assessments

- Screening

Within 21 days of treatment: tumor assessment, e.g. MRI, CT or x-ray
Within 14 days of treatment: history and physical examination, pregnancy test and routine x-rays
Within 7 days of treatment: VS, KPS, laboratory data, QoL

- On Study

Tumor assessments are scheduled every 6 weeks on both arms. QoL and laboratory data are obtained at least prior to each cycle. For population PK, blood samples are drawn on days 22 and 64 within the time windows 0.5 - 1.5 hours, 1.5 - 3 hours and 3 - 5 hours after drug administration.

- Visit Days

Capecitabine: 1, 8, 22, 43, 64, 85, 106, 127, 148, 169, 190, 211
5-FU/LV: 1, 15, 29, 43, 57, 85, 113, 127, 141, 169, 197, 211

Reviewer Comment: *Despite different lengths of cycles (3 vs. 4 weeks for capecitabine and 5-FU/LV arms, respectively), the timing of evaluations was nearly identical. Patients on 5-FU/LV had one additional laboratory evaluation (week 19); this resulted in both groups having12 laboratory evaluations at the end of week 30 when patients were considered for "continuation." This was not the case with QoL assessments which were obtained prior to each cycle, resulting in more timepoints for patients randomized to the 3-week (capecitabine) rather than the 4-week cycle (5-FU/LV).*

7.1.8 Efficacy Criteria and Study Endpoints

- **Tumor Response Criteria**

All patients entered were to have at least one bidimensionally measurable lesion. Objective responses were defined by the WHO criteria.

- **Time to Event Endpoints**

Time to Response is calculated from time of randomization to date of first response.

Duration of objective response (CR + PR) will be calculated according to the WHO criteria. Duration of a CR starts from the date the CR was first recorded to the date of PD. However, duration of a PR starts from the first day of treatment to date of PD. Patients for whom there is no follow-up information on survival or PD will be censored at study day 1.

Time to progression (TTP) is measured from time of randomization to time of PD or death if the patient dies due to causes other than PD, or the last date the patient was known to be progression free (censoring).

Survival will be calculated from the time of randomization to the date of death or the last date the patient was known to be alive.

Time to onset of the first grade 3-4 adverse event will be tested for diarrhea, stomatitis, nausea, vomiting, alopecia, leukopenia and hand-foot syndrome.

H_0: $ORR_{cap} \leq ORR_{5\text{-}FU/LV} - 10\%$ vs. H1: $ORR_{cap} > ORR_{5\text{-}FU/LV} - 10\%$

In addition, the proportion of patients with at least one grade 3-4 adverse event of this type will be tested using a χ^2-test with Schouten correction (two-sided).

- **Populations for Analyses**

The **intent -to-treat (ITT)** population ~~is defined as all patients who received at least one dose of drug~~ consists of all randomized patients.

The **standard** population consists of the ITT population excluding:

--Patients who do not receive drug
--Patients who receive less than 42 days (6 weeks) of therapy (except patients who withdrew from treatment due to PD or death
--Patients who receive less than 50% of the anticipated test treatment during the first 6

weeks.
--Patients with a major violation of the inclusion/exclusion criteria.
--Patients with inadequate tumor assessment information.
--Patients with inadequate information about tumor burden at baseline.

- **QoL**

The EORTC QLQ-C-30 will be given at baseline and prior to each cycle.

7.1.9 Safety Assessments and Dose Modifications

- **Grading of Toxicities**

Toxicities were graded by the NCIC version of the Common Toxicity Criteria. "Hand-foot" syndrome (palmar-plantar erythrodysesthesia) was graded according to the following toxicity measure.

Grade	Clinical Domain	Functional Domain
1	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema	Discomfort which does not disrupt normal activities
2	Painful erythema, with swelling	Discomfort which affects activities of daily living
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living

- **Dose Modification**

Capecitabine. If grade 2 to 4 toxicity occurs in patients receiving capecitabine, the following treatment interruption will occur.

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0-1 then continue at same dose with prophylaxis where possible	[redacted]	Discontinue treatment unless Investigator considers it to be in the best interest of the patient to continue at 50% of the original dose once toxicity has resolved to grade 0-1 (after approval of Clinical Leader)
2nd appearance of same toxicity	[redacted]	[redacted]	
3rd appearance of same toxicity	[redacted]	Discontinue treatment - off study	
4th appearance of same toxicity	Discontinue treatment - off study		

[redacted] = First level dose reduction to 75% of baseline dose
= Second level dose reduction to 50% of baseline dose

For grade 2/3 diarrhea, nausea or vomiting, capecitabine should be stopped and the patient treated symptomatically -- Imodium was recommended. If controlled within 2 days, capecitabine could

be restarted at 100% doses. If recovery takes > 2 days, dose modification according to the above table would occur.

5-FU/LV. 5-FU could be escalated by 10% of the preceding cycle's dose if no significant toxicity occurred. Dose modification for toxicity should be instituted according to the following table.

Dose Modification Based as a % of Preceding 5-FU Dose					
Hematologic Toxicity	Non-Hematologic Toxicity				
	0	1	2*	3*	4*
0	110	100	[redacted]		
1**	100	100	[redacted]		
2**	100	100	[redacted]		
3**	[redacted]				
4**					Withhold No further rx

*Hold until toxicity resolves
**Hold until granulocytes ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L

[redacted] = First level dose reduction to 80% of baseline dose
[redacted] = Second level dose reduction to 70% of baseline dose

Reviewer Comment: Note that both first and second level dose reductions for capecitabine are greater than for 5-FU/LV. This schema may have introduced bias into the comparative incidence and frequency of adverse events.

Premature withdrawal. The protocol states that patients could be withdrawn for an intercurrent illness, adverse event, treatment failure, protocol violations, cure, administrative reasons or other reasons.

7.1.10 Statistical and Analytical Methodology

- Sample Size

The sample size was powered for the primary analysis of at least equivalence in response rate defined as not worse than 10%. "... it is assumed that the overall response rate under the alternative hypothesis in the 5-FU/LV arm is 20% as well as in the capecitabine arm. With 262 evaluable patients per treatment arm there is a power of 80% to demonstrate at least equivalence between the two arms at an α-level of 2.5% and an equivalence definition of 10%. Assuming a drop-out rate of 15%, 302 patients per treatment arm should be enrolled....Assuming a response rate of 20% in the 5-FU + leucovorin arm and 30% in the capecitabine arm under the alternative hypothesis, then 302 patients evaluable for the intent-to-treat analysis in each treatment arm is also sufficient for testing the second primary hypothesis for difference..."

- Efficacy

At least equivalence in response rate would be tested with a 10% equivalence range (using a modified one-sided x^2 - type test with a Hauck-Anderson correction) for overall RR. If this test is significant, a two-sided x^2 - test for difference (with a Schouten continuity correction) will be used at the 5% level.

TTP will be evaluated by a 2-sided logrank test at a 5% α-level for a difference between the arms. The study had a power of 82% to 99% to detect a true difference of 4-5 weeks in median TTP favoring capecitabine.

In addition, Cox regression analyses would be considered exploratory analyses for TTP and survival. [redacted]

evaluate are HR ≤ 1.2 versus HR > 1.2. The test will be applied at the 2.5% level. The test will be positive if the upper limit of the 95% CI for the HR is not exceeding 1.2. This in turn, would prove that the risk of progression with capecitabine treatment is at most increased by 20% or better. In a second step, center groups (as used for randomization), the number of metastatic sites and the KPS will be added to the model. Additional factors would be tested for their influence; those significant at the 15% α-level in a model including only this factor will be used in a multivariate model. Factors not significant at the 5% level will be excluded from this model. Potential factors to be tested include sex, primary site, center, differentiation, prior adjuvant therapy (yes/no) and occurrence of liver metastases.

A further subgroup analysis is looking at the overall RR in patients with and without prior adjuvant therapy. RR and their 95% C.I. will be calculated in each subgroup.

Equivalence in survival will be tested by comparing if the upper limit of the HR is below 1.2 [illegible]: $H_0 \geq$ [illegible] vs. $H_1 <$ [illegible]. The underlying Cox regression model will keep only treatment as a factor.

QoL data from the EORTC-QLQ-C-30 questionnaire will be reported in summary tables over time. Missing values will be replaced by the last available observation after baseline. The primary timepoint for the analysis will be day 169, chosen to favor patients able to receive a longer administration and to account for possible bias due to patients with PD or early termination. The following hypothesis will be tested: H_0: $QoL_{cap} = QoL_{5\text{-}FU/LV}$ vs. H_1: $QoL_{cap} \neq QoL_{5\text{-}FU/LV}$. A comparison of the two treatments will be made using a two-sided Fisher-Yates [illegible] Van der Waerden test.

A longitudinal analysis will be applied for the global health score (items 29 and 30) obtained from the EORTC QLQ-C-30 questionnaire in order to explore the impact of missing values on the analysis of treatment effects. A random effect or covariance pattern models will be used with a polynomial model for the trend effect. The best covariance structure (among AR(1), compound symmetry, independence and several random factors intercept and slope) will be specified during analysis on the basis of the Akaike information. For the analysis of the dropout pattern, a pattern mixture model will be employed (Little 1993).

- Interim Analysis

No interim analyses were planned.

Reviewer Comment: *The NDA states interim analyses on safety data only were performed: one for initial filing for accelerated approval for the breast cancer indication and the second for 4-month safety update. Two analyses on survival were performed for preNDA meetings in addition to several survival analysis presented in the NDA—see below.*

7.2 Trial Results

7.2.1 Conduct of the Study

- **Informed Consent**

The study was conducted in accordance with the Declaration of Helsinki; patients gave written informed consent.

- **Randomization**

Randomization was assigned by country, using a block size of 6. The U.S. was stratified by 4 regions: North Central, Southern, Northeast and Western. The number of patients enrolled by

arm and country appears to be balanced (see Reviewer Table 2). The mean (2 days) and median (3 days) number of days between randomization and start of study drug was the same in both arms.

- **Efficacy Review Committee**

Radiographs (x-rays or scans) obtained in the first 48 weeks of treatment were submitted for review by an independent review committee (IRC) blinded to treatment arm and investigator assessment.

- **Protocol Violations**

Protocol violations (defined in this submission as failure to meet eligibility criteria) were classified as major or minor. Two patients had major protocol violations, the lack of histologically or cytologically confirmed cancer and were excluded from the "standard" population (see section 7.2.3.4). One of these patients, #17695/0525, was randomized to 5-FU/LV but did not receive treatment. The other patient, #17686/0355 was randomized to, and received, capecitabine.

Ninety-two patients were considered to have had minor protocol violations; 88 of these were identified prior to entry and granted a waiver from the sponsor to enter the study.

- **Quality Assurance**

A summary of the QA process is described in volume 112, p. 4 and appears adequate.

- **DSI Audits**

Three centers were audited by DSI – _____ Minor violations were found in each site; however, DSI concluded that the data appear acceptable to support an sNDA. (Ref: Clinical Inspection Summary dated June 22, 2000.)

7.2.2 Enrollment, Disposition, Demographics, Baseline Characteristics

- **Enrollment**

A total of 605 patients were randomized to treatment in 4 countries at 61 sites.

Reviewer Table 2*
Enrollment by Country (SO14695)

Country	# Centers	Randomized to Capecitabine	Randomized to 5-FU/LV	# Pts
U.S.	48	203	202	405
Canada	9	82	82	164
Brazil	2	10	9	19
Mexico	2	8	9	17
Total	61	303	302	605

*Derived from data in Sponsor's Appendix I, vol. 1, p. 179 and vol. 112, p. 90.

Seventy percent of the patients were entered from the U.S. The single site with the smallest accrual entered 1 patient; the site with the greatest accrual (Dr. Richard Pazdur, the principal investigator) entered 73 patients (12%). Eighteen centers accrued ≥ 10 patients.

- **Disposition**

The median duration of treatment was 115 days for patients receiving capecitabine and 131 days for patients randomized to 5-FU/LV. Information on disposition is derived from the Study Completion

form of the CRF (vol. 53) which provided 8 categories for coding reasons for withdrawal. The sponsor's Table 13 combines Violation of Selection Criteria and Other Protocol Violation. Data is collected and presented only up to 48 weeks on treatment (i.e., during the treatment and continuation phases).

Sponsor Table 13 (Abridged)*
Disposition (SO14695)

Reasons for Withdrawal	Capecitabine (N = 302)		5-FU/LV (N = 303)	
	No.	%	No.	%
Insuff. Therapeutic Response (PD)	188	62.3	177	58.4
AE/Intercurrent Illness	39	12.9	32	10.6
Patient Refusal	11	3.6	29	9.6
Death	9	3.0	11	3.6
Violation of Selection Criteria plus Other Protocol Violation	-	-	3	1.0
Admin/Other	5	1.7	9	3.0
Failure to Return (Lost to F/U)	-	-	2	0.7
Subtotal	252	83.4	263	86.8
Randomized but not Rx'd	3	1.0	9	3.0

+Vol. 50, p. 58

- **Demographics**

The following table, derived from Sponsor's Table 18, presents demographics of the study by arm. The majority of patients were male: 60% on capecitabine and 65% on 5-FU/LV. The arms were balanced with regard to age (median 64 years on capecitabine, 63 on 5-FU/LV); race (84 % caucasian in both arms); KPS (median 90% on both arms); and body surface area (mean and median 1.8 m^2).

Sponsor's Table 18 (Abridged) *
Baseline Demographics (SO14695)

	Capecitabine (N = 302)	5-FU/LV (N = 303)
SEX		
N	302	303
Males	181 (60%)	197 (65%)
Females	121 (40%)	106 (35%)
AGE (yr)		
N	302	303
Mean	62.4	62.1
SD	11.3	10.4
Median	64.0	63.0
Range	23 - 86	24 - 87
RACE		
N	302	303
Caucasian	255 (84%)	256 (84%)
Black	28 (9%)	24 (8%)
Oriental	2 (<1%)	4 (1%)
Hispanic	9 (3%)	14 (5%)
Other	8 (3%)	5 (2%)
Karnofsky PS		
N	298	281
Mean	88.3	88.5
SD	10.0	9.8
Median	90.0	90.0
Range		
Body Surface Area (m^2)		
N	300	301
Mean	1.866	1.857
SD	0.247	0.245
Median	1.860	1.850
Range		

*Vol. 50, p. 62

- **Baseline Characteristics**

The following table presents baseline disease characteristics of potential prognostic significance by arm. No imbalances are noted at the 0.05 significance level. More patients randomized to 5-FU/LV (36.3%) received prior adjuvant 5-FU-based chemotherapy compared to those randomized to capecitabine (27.8%).

Reviewer Table 3*
Baseline Characteristics (SO14695)

	Capecitabine	5-FU/LV
Interval Between Metastatic Disease & Randomization		
Mean ± SD	86.8 ± 132.9	92.4 ± 158.4
Median	48	46.5
Range		
Location		
Colon	222 (73.5%)	232 (76.6%)
Rectum	79 (26.2%)	70 (23.1%)
Tumor Differentiation[1]		
Well diff.	28 (9.3%)	24 (8.0%)
Mod. diff.	185 (61.3%)	198 (65.4%)
Poorly diff.	62 (20.5%)	54 (17.8%)
Undetermined/unknown	25 (8.3%)	25 (8.3%)
No. of Pts. by No. of Metastatic Sites		
1	46	43
2	66	60
3	75	77
4	48	52
5	27	29
>5	40	42
Most Frequent Sites of Metastases		
Liver		
Multiple	206 (68.2%)	202 (66.7%)
Solitary	26 (8.6%)	23 (7.6%)
None	63 (20.9%)	70 (23.1%)
Unknown	7 (2.3%)	8 (2.3%)
Lymph nodes		
Multiple	94 (31.1%)	102 (33.8%)
Solitary	22 (7.3%)	21 (6.9%)
None	171 (56.5%)	158 (52.1%)
Unknown	15 (0.3%)	22 (7.3%)
Lung		
Multiple	85 (28.1%)	88 (29.0%)
Solitary	22 (7.3%)	19 (6.3%)
None	194 (64.2%)	193 (63.7%)
Unknown	1 (0.3%)	3 (1.0%)
Prior Treatment		
Surgery	273 (90.4%)	270 (89.1%)
XRT	52 (17.2%)	62 (20.5%)
Adjuvant 5-FU	84 (27.8%)	110 (36.3%)

*Derived from Sponsor's Tables 19, 20, 21, 22, 23 in vol. 50 pp. 63 - 66.
[1]N = 300 for capecitabine and 301 for 5-FU/LV. Per sponsor, one patient in each group lacked histologic verification. Three patients still unaccounted for, but overall analyses would not be affected.

APPEARS THIS WAY
ON ORIGINAL

7.2.3 Efficacy Results

7.2.3.1 Response Rate

- **Investigator, IRC and Reconciled Determinations of RR**

The protocol specified that efficacy analyses of response rates, response durations, and TTP were to be based on the IRC's assessments. The IRC's assessment, although blinded, was criticized for limiting efficacy determinations to a subgroup of patients with radiographically measured lesions and/or to subgroups of lesions within a patient. At the preNDA meeting February 16, 1999, the FDA asked the sponsor to "reconcile" any differences between the investigator and IRC in order to both arrive at a single determination of efficacy and to provide clarity about sources of disagreements. The sponsor agreed and developed an algorithm to resolve differences between the investigator and IRC (see below). In reconciling differences, the sponsor further notes in the NDA that the IRC's assessment was limited not only by the absence of data on clinical progression but also because the IRC did not review data beyond week 48 of treatment. In the end, the sponsor notes that the IRC reviewed approximately one-half of the total number of events that would count as PD.

There were 164 disagreements (27%) between the investigator and IRC, 89 in patients receiving capecitabine and 75 in patients receiving 5-FU/LV.

- **Methodology for Reconciliation**

Responses were reviewed by the sponsor, who was blinded to treatment arm, using tumor measurements and comments provided by the investigator and IRC. When there were disagreements, the following algorithm was followed:

(a) In cases where PD followed the original protocol definition of PD, e.g., progression defined by a single lesion rather than the overall sum or progression of 25% in small lesions < 2 cm^2, PD was assessed according to the guidelines provided in the amendment.
(b) If the investigator commented that there was definite progression by clinical or biochemical parameters, this was accepted over IRC assessments limited to radiographs.
(c) If either (but not both) the investigator or IRC noted new lesions, PD was assigned.
(d) If no "post-baseline" assessments were available (e.g., refusal of treatment), the response field was left blank with comment as to why. Assessment of PD was determined if possible from follow-up and post-study chemotherapy information.
(e) For cases where assessments were incomplete (e.g. IRC able to assess only 1 of 3 indicator lesions), then the assessment that was more complete would be followed unless other over-riding situations arose (e.g., clinical PD). This includes those situations where no assessments were present, e.g., due to inappropriate test method which IRC could not assess.
(f) For borderline cases of response by only one of the assessors (i.e. only IRC or only investigator), the other assessment would generally be followed unless other over-riding evidence was present. For example, if investigator reported a SD throughout the entire study whereas IRC had PR with a 52% reduction, then the investigator assessment would be followed.
(g) If outlying single measurements that did not follow the logic of the case were noted (e.g. 6 sets of measurements throughout the study being very similar with one set in the middle being high enough to cause PD, or an outlying previous low measurement causing the early assessment of PD, then these would be ignored with a relevant comment being added.

(h) If PD was not documented (e.g. no baseline assessment or SD as the only assessment) then data from follow-up care and treatment was reviewed. If a date of PD was found or the patient started new chemotherapy, this date would be entered.
(i) If an incorrect assessment was assigned without a clarifying comment (e.g. miscalculation of measurements) this would be taken into account when comparing the assessment to the other assessment.
(j) For CR, if doubt existed on either side that a CR had been achieved (i.e., other disease described in the comments), the worst case scenario would be followed.

All three determinations of response rate (investigator, IRC and reconciled) are displayed in Reviewer Table XXX); however, the Agency considers the response rate after reconciliation to be the most reliable (and the sponsor submits the reconciled RR for labeling). The sponsor makes the point that capecitabine has met criteria for non-inferiority and is statistically superior to 5-FU/LV in each of the three determinations. Response rates are lowest for both treatment arms in the reconciled assessment, i.e., under closest scrutiny, and are approximately 25-30% lower than the investigator's assessment.

Reviewer Table 4*
Response Rate (ITT Population; SO14695)

	Capecitabine		5-FU/LV	
Investigator Assessment				
N	302	100%	303	100%
RR	75	25%	47	16%
CR	3	1%	3	1%
PR	72	24%	44	14%
SD	146	48%	158	52%
PD	57	20%	59	20%
Missing post-baseline information[1]	22	7%	38	12%
χ^2		p = 0.005		
IRC Assessment				
N	269	100%	266	100%
RR	78	26%	35	12%
CR	1	0.3%	1	0.3%
PR	77	26%	34	11%
SD	148	49%	181	60%
PD	43	14%	36	12%
Missing post-baseline information[1]	30	10%	49	16%
χ^2		p = 0.0001		
Sponsor ("reconciled") Assessment				
N	302	100%	303	100%
RR	63	21%	34	11%
(95% CI)		(16.42, 25.89%)		(7.9%, 15.33%)
CR	0	–	1	0.33%
PR	63	21%	33	11%
SD	147	49%	157	52%
PD	66	22%	65	21%
Missing post-baseline information[1]	24	8%	46	15%
Insufficient info to allow reconciliation	2	0.66%	1	0.33%
χ^2		p = 0.0015		

*Data derived from Sponsor's Table 25 and 27, vol. 31, p. 64 - 65; Table 3, vol.118, p. 8.
[1]Defined as patients who were withdrawn or died before 42 days; counted as nonresponders.

Reviewer Comment: *Eligibility criteria required at least one bidimensionally measurable lesion. Cross-reference of Listing 2.1 (Patient Listing of Lesion Description – Investigator; vol. 63), 2.5 (Patient Listing of Lesion Description – IRC; vol. 64) and Appendix 9 (List of Violations; vol. 50) indicates that all patients were thought to have had bidimensionally measurable disease at baseline. This percent of patients with measurable disease in a phase 3 trial is unusual; the percent with measurable disease in the trial supporting approval of leucovorin was 33% (Poon MA, et al. J Clin Oncol 7:1407-1417, 1989). It should be noted that this accounting does not address minimum lesion size or adequacy of technique to measure the lesion.*

A random sample of CRFs from responders was reviewed. No disagreements were found with the reconciled assessment as provided in Appendix 1: Listing of Tumor Response by Patient—Reconciled data (vol.118, pp. 16-58).

A remaining concern is the impact of "missing post-baseline information" on the claim of superiority for capecitabine on the endpoint of RR. Between 7-8% of patients on capecitabine and 12-16% on 5-FU/LV had "missing post-baseline data." In a worse case scenario analysis, when all patients with missing data on the control arm are counted as responders, the reconciled RR for 5-FU/LV becomes 26% and surpasses the RR of 21% for capecitabine. It could be reasonably argued that this would be an unlikely scenario since the RR to 5-FU/LV is typically in the range of 15-20% (Kelson, David. Surrogate endpoints in assessment of new drugs in colorectal cancer. Lancet 2000;356: 353-354). One would have to argue that responders in particular were excluded. Therefore, reasons for missing data were reviewed.

As background, the NDA defined "missing post-baseline information" as patients who were withdrawn or died before 42 days, which is when the first tumor assessments were scheduled. In June 30, 2000 correspondence, the sponsor provided detailed information on patients counted as missing and is displayed in Reviewer Table 5 below. From this data, it can be seen that patients also were counted as missing data if reconciliation could not be made of a disagreement between investigator and IRC of response assignment. This involved 10 patients who were considered responders by either the investigator or IRC: 7 on 5-FU/LV and 3 on capecitabine.

Reviewer Table 5:
Reasons for Missing Post-Baseline Information (SO14695)

Reason	Capecitabine		5-FU/LV	
	Sponsor	FDA	Sponsor	FDA
Refused Rx	4	6 • #17685/0334 refused all rx • # 17695/1527 refused all rx	15	17 • #17679/0181 refused all rx • #17831/3007 refused all rx
Death	2	2	11	11
AE or Intercurrent Ill.	15	15	9	9
Insufficient Rx	1	0 • #17685/332 rec'd 173d of rx & considered PR by inv	2	0 • #17696/546 rx for 87d; SD by inv • #17703/1353 rx for 208d; PR by inv/SD by IRC
Violation	0	0	3	3
Admin/Other	0	0	1	0 • #17831/3007 refused all rx and is counted in that category
?	2	0 • #17714/945 & 17799/1006 rec'd > 300d of rx. Considered PR by inv but ineval by reconciled report.	5	0 • #17498/2002, 17701/641, 17801/1088, 17803/1185, 17814/724 rec'd 222-341d rx; no reconciled response assignment but PR by either inv. or IRC
TOTAL	24 (8%)	24 –3 +2 = 23 (8%)	46 (15%)	46–7+1 = 30 (10%)

The methodology for reconciliation (see algorithm above) generally invoked the worst case scenario in the event that no new information clarified the disagreement between the investigator and IRC. The 10 patients who fall into this category could then be counted as nonresponders and removed from the category of "missing data," as in fact there is data, simply no reconciliation. Alternatively, since there are more patients in this category on the 5-FU/LV arm and we wisd to perform a worst case scenario analysis, we could count these 10 as responders. The RR become 14% for 5-FU/LV and 22% on capecitabine, i.e. superiority for capecitabine still stands.

The other source of imbalance in missing data between the treatment arms is in the number of patients refusing treatment. It should be noted that this was an unblinded trial and that capecitabine is commercially available which may have contributed to 9 patients on 5-FU/LVrefusing all treatment vs. 3 randomized to capecitabine.

- **Concomitant "Anticancer" Treatment**

The protocol section, "Concomitant Medication and Treatment," did not explicitly prohibit other anticancer therapy. However, the CRF required listing of all concomitant medications. The following table presents other treatment during study that could potentially be considered "anticancer," including radiotherapy (XRT). Excluded are treatments started after the last date of study drug or within the last week of study drug.

Reviewer Table 6*
Patients who received Concomitant Treatment with Potential Anticancer Agents (SO14695)

	Capecitabine Pt #: Measurable Disease	Best Response	5-FU/LV Pt #: Measurable Disease	Best Response
Shark Cartilage	2 #17703/207: liver; also on accolate (leukotriene-receptor antagonist) #17703/1351: liver, pleura, peritoneal	 PR SD	7 #17714/948: pelvic mass #17818/1063: liver, LN #17703/1387: liver, lung, adrenal #17802/1139: liver #17804/1202: liver #17830/1301: liver #17704/718: liver	 SD SD SD PR SD SD SD
Progestogens	19		27	
Bisphosphonates	4 #17695/527: N/A #18815/1234: liver . #17799/1008: RPLN (for osteoporosis) #17692/495: RPLN (Hyperca++)	Randomized, not rx PR PR SD	0	
Chemotherapy	1 #17715/988: Intrapleural bleomycin for effusion; indicator lesions = measurable parenchymal lung.	SD	0	
XRT	0		0	

Data derived from June 30, 2000 correspondence; list 2.1, vol. 62; list 2.2, vol. 63; list 2.5, vol. 64; reconciled response data, vol. 118

Reviewer Comment: *In all cases of treatment with bisphosphonates, lesions other than bone were followed. Progestogens included megace, provera, prempro. The only patient administered chemotherapy (bleomycin) had intracavitary administration to nonmeasurable disease. None of the treatments are approved for colorectal cancer and are not considered to be confounding.*

- **Exploratory Analysis: Response Rates in Subgroups**

The sponsor conducted exploratory analyses of response rate in a variety of subgroups: center size (≤ 10 or > 10 patients), number of metastatic sites at baseline (1 vs. 2 vs. 3 vs. 4 vs. >4), age (≤ 60 or > 60), predominant site of metastasis (liver vs. lung vs. soft tissue vs. other visceral), colon vs. rectal primary, race (caucasian vs. back vs. other) and prior adjuvant chemotherapy. RR with capecitabine were higher in all subgroups except in the category of race designated "other."

Reviewer Comments:

1. *Marketing materials state "superior objective response rates vs. 5-FU/LV in a subgroup of patients from studies 1 and 2 who received prior adjuvant 5-FU." The RR in patients who received prior adjuvant chemotherapy was lower than the RR in chemotherapy-naive patients within both treatment arms (and in both phase 3 studies). No statistical significance is claimed. Although there was an imbalance in baseline factors with more patients who had*

received prior adjuvant therapy being randomized to 5-FU/LV, adjusting for the imbalance still leaves a significant p value for the overall RR.

2. *The higher RR with 5-FU/LV in patients with race classified as "other" is not seen in the predominantly foreign phase 3 trial, SO14796. The small number of patients (19 on capecitabine and 23 on 5-FU/LV) and the heterogeneity (hispanic, oriental, Native Americans and mixed ethnic groups) prevents any conclusions. The results with patients classified as "Black" (28 on capecitabine and 24 on 5-FU/LV) vary dramatically depending on the database, investigator vs. IRC. The foreign trial is noncontributory in this regard, having entered only 2 Black patients.*

7.2.3.2 Response Duration

The median duration of response for patients treated with capecitabine was 278 days; the median duration of response for patients treated with 5-FU/LV was 314 days. No comparison is attempted since responders represent selected nonrandomized subgroups.

7.2.3.3 Time to Progression

TTP was defined in the protocol as the time from randomization to disease progression or death, as determined by the reconciled database (see Section 7.2.3.1) and a database closure of January 24, 1999. Results are shown in Reviewer Table 7. There was no statistically significant difference between the treatment arms. The p-value for the log-rank test was 0.897.

Reviewer Table 7: TTP (S014695)

	Xeloda N = 302	5FU/LV N = 303
TTP		
# with PD	244	243
median ("reconciled")	4.3 mo.*	4.4 mo.
	128 days	131 days
95% CI	(120, 136)	(105, 153)
HR (Xeloda:5-FU/LV)	0.99	
95% CI	(0.84, 1.17)	

*Months calculated by days divided by 30.

Reviewer Comments:

1. *The sponsor states that the two treatment arms are equivalent based on the upper and lower bounds of the 95% CI of the HR. However, as discussed elsewhere in this review (assessment of survival and in Appendix II: FDA Non-inferiority Analyses), a claim for non-inferiority requires demonstration that a clinically meaningful fraction of the treatment effect of 5-FU/LV vs. 5-FU is preserved.*
2. *The sponsor performed an exploratory Cox regression analysis for TTP adjusting for selected baseline characteristics and prognostic factors, the majority of which were specified in the protocol. Other than KPS 70% vs. 100% and presence of liver metastases, covariates selected varied by whether the database used was the investigator's or IRC's.*

7.2.3.4 Survival

Results

Overall survival was measured from the date of randomization until the date of death. The results for overall survival based the January 24, 1999 and the requested survival update (May 15, 2000 cutoff) are shown in Reviewer Table 8.

Reviewer Table 8:
Overall Survival (ITT analysis; S014695)

	Xeloda	5FU/LV
[illegible]		
Survival		
• **Median**	12.6 mo.* 378 days	13.3 mo. 400 days
95% CI	(318, 432)	(356, 444)
# Events	190 (62.9%)	188 (62.0%)
• **HR** (Xeloda:5-FU/LV) 95% CI	1.13 (0.92; 1.38)	
Requested Updated Survival Analysis - Cutoff Date May 15, 2000		
Survival		
• **Median**	12.7 mo. 380 days	13.6 mo. 407 days
95% CI	(321, 434)	(366, 446)
# Events	260 (86%)	273 (90%)
• **HR** (Xeloda:5-FU/LV) 95% CI	1.00 (0.84, 1.18)	

* Months calculated by days divided by 30.

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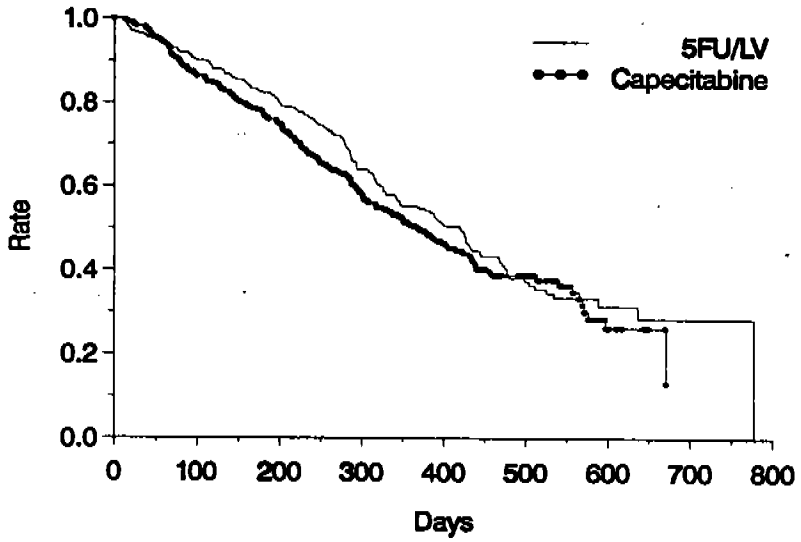
The Kaplan Meier estimates for survival based on the cutoff date of January 24, 1999 are shown in Reviewer Figure 2.

Reviewer Figure 2

Survival Curves for Study SO14695



- **Protocol-Defined Exploratory Analysis: Survival in the "Standard Population"**

The sponsor prospectively defined an evaluable patient population ("standard" -- see Section 7.1.8 of the protocol review) for exploratory analyses. Of the 605 patients randomized, 33 (10.9%) on capecitabine and 37 (12.1%) on 5-FU/LV were excluded from the standard population leaving a total of 535 patients. Reasons for exclusion are displayed in Sponsor Table 17.

Sponsor Table 17*:
Summary of Reasons for Exclusion from Standard Population (SO14695)

Reason for Exclusion	Capecitabine (N = 269)	5-FU/LV (N = 266)
Did not receive treatment	3	9
Rcd < 6 wks of Rx w/o PD or death	16	18
Rcd < 50% of rx in first 6 wks	7	3
Inadequate tumor assessment	7	7
Major protocol violation	1	--
Total	**33**	**37**

*Vol. 50, p. 60.

Reviewer Comment: *Cross-reference of protocol violations (Appendix 11, vol. 112) with patients excluded from the standard analysis (Appendices 10, vol. 112) shows consistency in rationale for exclusion of patients from both arms. The reason for exclusion of inadequate tumor assessment*

would not be necessary for an analysis of survival, although it may be reasonable for testing non-inferiority of response rates. It should also be noted that the standard population represents a nonrandomized subgroup of the overall trial population whether this subgroup remains balanced for known and unknown prognostic factors is uncertain.

Analysis in the standard population is of interest since the ICH E9 guidance raised the issue that an ITT analysis is not conservative when testing for non-inferiority. There appears to be comparable dropout per arm. The following analysis provided by the sponsor (not confirmed by the FDA) is exploratory. The log rank test p value is 0.54.

Reviewer Table 9:
Overall Survival (Standard Population; S014695)

	Xeloda (N = 269)	5FU/LV (N = 266)
Survival		
• **Median**	13.0 mo.*	14.0 mo.
	391 days	419 days
95% CI	(345; 440)	(356; 467)
# Events	164 (61%)	161 (60%)
• **HR** (Xeloda:5-FU/LV)	1.07	
95% CI	(0.86, 1.33)	

- Months calculated by days divided by 30.

Reviewer Comment: *Results are similar to the ITT analysis with upper bounds of the 95% CI for the HR of 1.33 for the standard population and 1.38 for the ITT population.*

- **Protocol-Defined Exploratory Analysis: Cox Regression for Prognostic Factors, Including Age and Gender**

The protocol had specified a Cox regression analyses on TTP, stratifying for the following covariates: country, large (>5 patients) vs. small centers, gender, differentiation, liver metastases, predominant site of disease at baseline, number of metastatic sites at baseline, location in the colon vs. rectum, KPS, age, race, number of prior regimens and prior adjuvant therapy. These same covariates were used in a Cox regression analysis on survival. A multivariate analysis was performed including all covariates seen as significant at the 15% level in the univariate analysis. The least significant factor was excluded from the model until all factors were significant at 5% (final multivariate model). Seven factors were retained in the model. In the order of most significant to least, they are: country: Mexico; KPS 70% vs. 100%; KPS 80% vs. 100%; one vs more metastatic sites; liver as the predominant site; colon vs rectal primary; and race "other" which also had a treatment interaction.

Reviewer Comments:

1. *Factors retained in the final multivariate model varied amongst TTP as assessed by the investigator, TTP as assessed by the IRC and survival. KPS of 70% vs. 100% was the only factor common to all three analyses. Furthermore, the definition of a large center was > 10 patients when the sponsored performed subgroup analyses for the protocol-specified analysis of response rate. These analyses should be considered exploratory.*
2. *The category of race coded "other" includes Asians (#8), Hispanics (#23) and Other Americans such as Native Americans (#11). Due to the small numbers overall as well as the heterogeneity of this group, it is difficult to generate hypotheses or conclusions.*

- **Chemotherapy after Study Drug**

Sponsor Table 26 presents number of patients who received additional chemotherapy after study treatment. Data are not available for 16 patients: 4 with missing data and 12 still on study drug at the time the forms were requested. Twelve of the 16 were receiving capecitabine and 4, 5-FU/LV. Slightly more patients randomized to 5-FU/LV received subsequent CPT-11, the only agent that has been shown to prolong survival as second-line treatment of colorectal cancer. No tests of significance are performed.

Sponsor Table 26:
Post-Study Chemotherapy (SO14695)

Post-Study Chemotherapy	Capecitabine (N = 302)	5-FU/LV (N = 303)
Total Receiving Chemorx	60.9%	63.7%
CPT-11	38.1%	43.6%
5-FU	35.7%	29.0%
Oxaliplatin	1.7%	5.3%

Reviewer Comment: *The absence of important details such as dose, specifics of 5FU administration (e.g. with leucovorin or as a continuous infusion), duration of therapy and whether given as second or later treatment, limits any serious analysis. The sponsor submitted more detailed information addressing these issues in the Four-Month Safety Update. Second line treatments were isolated, along with study day initiated, treatment duration and cumulative dose. The number of patients receiving CPT-11is 69 and 88 on capecitabine and 5-FU/LV, respectively. Other parameters are between the arms are similar. No obvious bias in favor of capecitabine is seen with these data as more patients on the control arm received CPT-11..*

Major Statistical Issue: Testing a Non-Inferiority Hypothesis

The protocol-specified test of non-inferiority in survival was defined quantitatively by the upper bound of the 95% CI of the HR of capecitabine to 5-FU/LV. If the upper limit did not exceed 1.25 while testing at the 2.5% α-level, non-inferiority would be concluded.

The appropriateness of such a fixed margin depends on whether it represents preservation of a clinically relevant fraction of the survival benefit of the active control (5-FU/LV). Neither of the two randomized trials of capecitabine vs. 5-FU/LV could include a third arm of 5-FU, placebo or best supportive care arm for ethical reasons. Therefore, the body of literature of randomized trials of 5-FU with and without leucovorin for the first line treatment of metastatic colorectal cancer must be used to determined the magnitude of the survival benefit of 5-FU/LV.

Reviewer Table 10 shows a set of clinical trials that have compared survival between 5-FU and 5-FU/LV for first line treatment of colorectal cancer. Trials were included in the meta-analysis if the design included randomization to a 5-FU regimen of 5 sequential days with or without leucovorin, crossover was prohibited and survival was an endpoint. A meta-analysis was performed using a random effect model using results from all ten papers (trials).

Reviewer Table 10: Historical Trials of 5FU/LV (10-Paper Meta-Analysis)

Study (Author)	Data Sources	FDA's Data Abstraction	
		Ln(HR)[1]	Std
Doroshow	HR given in paper	.301	.232
Erlichman	HR given in paper	.235	.188
DiCostanzo	136 death,p=0.14	-.253	.171
Labianca	171 death,p>0.3	.143	.153
Poon (HDLV)	HR given	.329	.185
Poon (LDLV)	HR given	.300	.184
Pallavincini	146 death, p=0.05	.324	.166
Borner	250 death, p=0.02	.294	.126
Leichman	HR given in the paper	.0296	.165
Loffler	135 death, p=0.0001	.670	.172
Overall:	Random Effect Model	0.234	0.075
		HR: 1.264	HR 95% CI: 1.091-1.464

[1] All hazard ratios are 5-FU/5-FU+LV

The question of whether a fraction of the survival benefit an active control is preserved can be asked in two ways: (a) is survival with capecitabine better than survival in patients treated with 5-FU alone (subsequently referred to as 0% retention of the 5-FU/LV effect); and/or (b) is a clinically relevant fraction of the effect of the active control, 5-FU/LV, preserved. Such a clinically relevant fraction of the effect of the active control on survival was not prospectively defined.

The hypothesis the Agency's analysis will be testing is that Xeloda retains at least 50% effect on survival with respect to hazard ratios due to adding LV to 5-FU (i.e., HR(Xeloda/5-FU) < (1+HR(5-FU+LV/5-FU))/2). Since there is no treatment arm of 5-FU alone, historical data are used to make statistical inferences about the 5-FU/5-FU+LV hazard ratio. If the HR(5-FU/5-FU+LV) is constant then the above hypothesis is equivalent to HR(Xeloda/5-FU+LV) < (1+HR(5-FU/5-FU+LV))/2 . It is this hypothesis that is formally tested using data from historical trials and those active-controlled Xeloda trials.

The non-inferiority margin (value for (1+HR(5-FU/5-FU+LV))/2) will be determined from a meta-analysis involving 10 papers. If the 97.5% confidence upper bound for the HR(Xeloda/5-FU+LV) lies below the non-inferiority margin, non-inferiority will be claimed.

Assumptions used for the analysis of the Xeloda trials

From mathematical calculations, using results from ten historical studies comparing survival between 5-FU and 5-FU+LV arms, the variance of the log-hazard ratio for these Xeloda studies (January 1999 cutoff), the belief that the effect on survival of adding LV has not changed and a desire to maintain 50% of the historical effect on survival contributed to the addition of LV, an approximate one-sided 2.5% type I error rate will be maintained by using the lower bound of the 30% two-sided confidence interval for the 5-FU/5-FU+LV hazard ratio to define the margin.

This 30% confidence coefficient is unique to these Xeloda studies. In other settings, those percent confidence coefficients whose lower bounds lead to an approximate one-sided 2.5% type I error rate will vary greatly among combinations of active-controlled trials and meta-analyses based on historical trials.

Reviewer Table 10: Historical Trials of 5FU/LV (10-Paper Meta-Analysis)

Study (Author)	Data Sources	FDA's Data Abstraction	
		Ln(HR)[1]	Std
Doroshow	HR given in paper	.301	.232
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Overall:	Random Effect Model	0.234	0.075
		HR: 1.264	HR 95% CI: 1.091-1.464

[1] All hazard ratios are 5-FU/5-FU+LV

The question of whether a fraction of the survival benefit an active control is preserved can be asked in two ways: (a) is survival with capecitabine better than survival in patients treated with 5-FU alone (subsequently referred to as 0% retention of the 5-FU/LV effect); and/or (b) is a clinically relevant fraction of the effect of the active control, 5-FU/LV, preserved. Such a clinically relevant fraction of the effect of the active control on survival was not prospectively defined.

The hypothesis the Agency's analysis will be testing is that Xeloda retains at least 50% effect on survival with respect to hazard ratios due to adding LV to 5-FU (i.e., HR(Xeloda/5-FU) < (1+HR(5-FU+LV/5-FU))/2). Since there is no treatment arm of 5-FU alone, historical data are used to make statistical inferences about the 5-FU/5-FU+LV hazard ratio. If the HR(5-FU/5-FU+LV) is constant then the above hypothesis is equivalent to HR(Xeloda/5-FU+LV) < (1+HR(5-FU/5-FU+LV))/2 . It is this hypothesis that is formally tested using data from historical trials and those active-controlled Xeloda trials.

The non-inferiority margin (value for (1+HR(5-FU/5-FU+LV))/2) will be determined from a meta-analysis involving 10 papers. If the 97.5% confidence upper bound for the HR(Xeloda/5-FU+LV) lies below the non-inferiority margin, non-inferiority will be claimed.

<u>Assumptions used for the analysis of the Xeloda trials</u>
From mathematical calculations, using results from ten historical studies comparing survival between 5-FU and 5-FU+LV arms, the variance of the log-hazard ratio for these Xeloda studies (January 1999 cutoff), the belief that the effect on survival of adding LV has not changed and a desire to maintain 50% of the historical effect on survival contributed to the addition of LV, an approximate one-sided 2.5% type I error rate will be maintained by using the lower bound of the 30% two-sided confidence interval for the 5-FU/5-FU+LV hazard ratio to define the margin.

This 30% confidence coefficient is unique to these Xeloda studies. In other settings, those percent confidence coefficients whose lower bounds lead to an approximate one-sided 2.5% type I error rate will vary greatly among combinations of active-controlled trials and meta-analyses based on historical trials.

For those two combinations of meta-analysis and Xeloda trials (SO14695 and SO14796; January 1999 cutoff), based on iterative calculations (ratio of variances of 1.891 and 1.844, respectfully) and those assumptions given above, when the upper 97.5% confidence bound is compared to the calculated margin, the approximate one-sided type I error rate - at 50% of the survival effect retained using the lower bound of a 30% confidence interval to calculate the margin - ranges from _____ to _____ The percent confidence coefficients whose 100γ% two-sided C.I. for HR(5-FU/5-FU+LV) have approximate 2.5% type I error range from 29.3% to 29.6%.

In the above case, when the upper 97.5% confidence bound is compared to the calculated margin, one-sided type I error rates - at 0% of the survival effect retained using the lower bound of a 48% confidence interval to calculate the margin - range from _____ to _____. The percent confidence coefficients whose 100γ% two-sided C.I. for HR(5-FU/5-FU+LV) have approximate 2.5% type I error range from 47.6% to 48.0%.

Survival Analyses

Table 11 below lists vital survival descriptive statistics for S014695 using both cutoff dates of January 1999 and May 15, 2000.

Reviewer Table 11: Summary of Relevant Survival Descriptive Statistics (SO14695)

Study	HR(Xeloda/5-FU+LV)	log HR	SE(logHR)
ITT Population			
SO14695 January 1999 cutoff	1.13	0.1220	0.1031
SO14695 May 15, 2000 cutoff	1.00	-0.0036	0.0868
Standard Population			
SO14695 May 15, 2000 cutoff	0.98	-0.0218	0.0926

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Table 12 below gives lower limits of various confidence intervals for the hazard ratio of 5-FU to 5-FU+LV. These limits will be used to define non-inferiority margins for analyses given in tables 13 and 14 and elsewhere.

Reviewer Table 12: Lower Limits of C.I.s for HR(5-FU/5-FU+LV)

Lower Limits of 100γ% C.I. for HR(5-FU/5-FU+LV)	
100γ%	**10 paper Meta-Analysis**
0%[1]	1.264
30%	1.228
32%	1.225
34%	1.223
39%	1.216
43%	1.211
45%	1.208
48%	1.204
52%	1.199
54%	1.196
60%	1.186
63%	1.182
65%	1.178
95%	1.091

[1] This row gives the point estimate of HR(5-FU/5-FU+LV).

Table 13 below gives results of the 0.025 one-sided type I error rate survival analyses (January 1999 cutoff) for the ITT population using the 10-paper meta-analysis.

Reviewer Table 13:
Non-inferiority Survival Analysis for SO14695 (January 1999 Cutoff) using the 10-paper Meta-Analysis and a 0.025 One-Sided Type I Error Rate (Margins and Results are Given)

Study	50% retained	0% retained
ITT Population		
SO14695		
97.5% confidence	1.114[1]	1.204[2]
upper bound = 1.38	NO	NO

[1] Margin is computed using the lower limit of the 30% C.I. for HR(5-FU/5-FU+LV).
[2] Margin is computed using the lower limit of the 48% C.I. for HR(5-FU/5-FU+LV).

Table 14 below gives results of a 0.025 one-sided type I error rate survival analyses (May 15, 2000 cutoff) using the 10-paper meta-analysis.

Reviewer Table 14:
Non-inferiority Updated (May 15, 2000 Cutoff) Survival Analysis for SO14695 using the 10-paper Meta-Analysis and a 0.025 One-Sided Type I Error Rate (Margins and Results are Given)

Study	50% retained	0% retained
ITT Population		
SO14695		
97.5% confidence	1.111[1]	1.196[2]
upper bound = 1.18	NO	YES
Standard Population		
SO14695		
97.5% confidence	1.113[3]	1.199[4]
upper bound = 1.17	NO	YES

[1] Margin is computed using the lower limit of the 34% C.I. for HR(5-FU/5-FU+LV).
[2] Margin is computed using the lower limit of the 54% C.I. for HR(5-FU/5-FU+LV).
[3] Margin is computed using the lower limit of the 65% C.I. for HR (5-FU/5-FU+LV).
[4] Margin is computed using the lower limit of the 52% C.I. for HR (5-FU/5-FU+LV).

For each population, a greater than 0% retention of the survival effect due to adding LV to 5-FU was statistically significant at a 0.025 one-sided significance level for the SO14695 trial.

For the ITT population of the SO14695 trial, the 97.5% lower bound for the percent of historical survival effect maintained is 9.6% (51.6% CI lower bound of 1.199; cutoff =1.18).

For the standard population, the S014695 trial, the 97.5% lower bound for the percent of historical survival effect maintained is 16% (46.7% C.I. lower bound of 1.206, cutoff = 1.173).

Table 15 below gives results of the CBER method survival analyses (January 1999 cutoff) for the ITT population using the 10-paper meta-analysis.

Reviewer Table 15:
Non-inferiority Survival Analysis for SO14695 (January 1999 Cutoff)
using the 10-paper Meta-Analysis and the CBER survival analysis method

Study	50% retained	0% retained
ITT Population		
SO14695		
97.5% confidence	1.045	1.091
upper bound = 1.38	NO	NO

Using this method led to no claim of non-inferiority.

Table 16 gives results of the survival analyses according to the CBER methodology using the 10-paper meta-analysis and the most recent updated survival analyses.

Reviewer Table 16:
Non-inferiority Updated (May 15, 2000 Cutoff) Survival Analysis for SO14695 using the 10-paper Meta-Analysis and the CBER survival analysis method

Study	50% retained	0% retained
ITT Population		
SO14695		
97.5% confidence	1.045	1.091
upper bound = 1.18	NO	NO
Standard Population		
S014695		
97.5% confidence	1.045	1.091
upper bound = 1.17	NO	NO

Based on the ITT population of SO14695, the largest percent maintained of the historical survival effect using the CBER Method is -98% (i.e., 5-FU is better than Xeloda by about as much as 5-FU+LV is better than 5-FU with respect to survival).

For the standard population of S014695, the largest percent maintained of the historical survival effect using the CBER Method is –90% (i.e., 5-FU is better than Xeloda by about as much as 5-FU/LV is better than 5-FU with respect to survival).

Table 17 gives the power at the time of the last death for the ITT population (assuming exponential distributions) when the true hazard ratio of Xeloda vs 5-FU+LV equals 1. Powers were calculated for 602 deaths (study 14796) and 1207 deaths (pooled studies).

Reviewer Table 17: Power at the Time of the Last Death

	One–Sided 0.025 Percent Retained		CBER Method Percent Retained	
Power at	**50%**	**0%**	**50%**	**0%**
602 deaths	25%	58%	8%	19%
1207 deaths	40%	80%	12%	33%

For each trial there was very low power to conclude at least 50% retention of the survival effect due to adding LV to 5-FU. For each Xeloda trial, at times prior to the death of the last patient, the power to make an association claim of more than 50% effect retained is at most 25% (8%) using the "One-sided 0.025" procedure (CBER method).

Table 18 gives the number of events (deaths) needed for each method to guarantee 80% power to claim non-inferiority when a drug yields the same survival distribution as 5-FU+LV. Many events are needed.

Reviewer Table 18: Number of Events (Deaths) Required for 80% Power

	One-Sided 0.025 Percent Retained		CBER Method Percent Retained	
	50%	0%	50%	0%
No. of Events	4460	1200	15840	4135

Eight-Paper Meta-Analysis Results

When a distribution is mound shaped or normal (symmetric with tails that decay many orders quicker than exponential decay), the sample mean is the best estimator of the point of symmetry in the distribution. The sample mean tends to be closer to the true mean than the sample median or any other trimmed mean. When a distribution is symmetric with exponential decaying tails the sample median has many optimal properties (the sample median is arguably the best estimator). For cases of symmetric distributions with tails between exponential decay and normal tails, a trimmed mean will be a better estimator of the point of symmetry.

The variability in the ten-paper meta-analysis is largely between study variability (as opposed to within study variability). Because the distribution of log-hazard ratios of 5-FU /5-FU+LV appears fairly symmetric with heavy tails (an outlying value in each tail) the largest and smallest log-hazard ratios were trimmed. An eight-paper meta-analysis was performed for sensitivity purposes (without any adjustment to resulting variance because of trimming). Results of an eight-paper meta-analysis are given in Table 19 below. All hazard ratios are 5-FU/5-FU+LV.

Reviewer Table 19: Results of the 8-Paper Meta-Analysis

log HR	SE(log HR)	HR	95% C.I.
0.23979	0.0593	1.271	(1.132, 1.428)

When these meta-analysis results are used in the non-inferiority survival analysis of the ITT population, the 97.5% lower bound for the percent of historical survival effect maintained is 22% (41.2% CI lower bound of 1.231; cutoff =1.18) for the SO14695 trial.

When these meta-analysis results are used for the non-inferiority survival analysis based on the standard population, the 97.5% lower bound for the percent of the historical survival effect maintained is 27% (35.2% C.I. lower bound of 1.237; cutoff = 1.173) for S014695.

For the ITT population, using the CBER Method the largest percent of historical survival effect maintained is –36% (i.e., 5-FU is better than Xeloda by 36% of the amount that 5-FU+LV is better than 5-FU, with respect to survival) for the SO14695 trial.

For the standard population and using the CBER Method, the largest percent of historical survival effect maintained is –31% (i.e., 5-FU is better than Xeloda by 31% of the amount 5-FU/LV is better than 5-FU, with respect to survival) in the S014695 trial.

7.2.3.5 Quality of Life

The protocol-specified instrument for measurement of QoL was the EORTC QLQ-C30. Subscales 29 and 30, measuring the global health status, were preselected as the primary outcome of interest over functional and symptoms scales. The timepoint for the primary analysis was day 169 (week 24), chosen to diminish the effect on early dropouts and deaths.

At day 169, 107 (35%) patients on capecitabine and 101 (33%) on 5-FU/LV were evaluated. The QoL global health scores were not statistically different for the two treatments (p = 0.7095). Descriptive analyses of the other domains, including appetite loss, fatigue, diarrhea, nausea and vomiting did not indicate a major difference between the treatments.

Reviewer Comment: *Due to both the high percentage of missing data and the different cycle lengths resulting in collection of QoL at different timepoints, these data should be interpreted with caution and be considered exploratory.*

7.2.4 Safety Results

The population evaluable for safety consists of 593 patients: 12 of the 605 randomized patients did not receive study medication and were not assessed for safety (3 to capecitabine, 9 to 5-FU/LV). The safety aspects of SO14695 are reviewed in the Integrated Summary of Safety (ISS; Section 11).

8. Pivotal Trial: Protocol SO14796

An open-label randomized phase III study comparing capecitabine with 5-fluorouracel in combination with leucovorin as first-line chemotherapy in patients with advanced and/or metastatic colorectal carcinoma

8.1 Protocol Review

This protocol and the CRF were identical to protocol SO14695 – refer to Section 7.1 for details.

Principal Investigator: Dr. Peter Harper

Reviewer Table 20: Protocol S014796 Milestones

Milestone	Date	# Pts Entered	Highlights/Comments
First Patient Randomized	October 2, 1996		
Amendment 1	August 12, 1997	257	Redefinition of PD from 25 to 50% ↑. Added details of a Cox regression analysis.
Amendment 2	November 10, 1998	602	Changes to statistical analysis plan. Clarified ITT analysis = all randomized pts. Added longitudinal analysis. Clarified noninferiority test for TTP or death.
Last Patient Randomized	February 4, 1998	605	
Original or "Clinical" Data Cutoff	August 24, 1998 Survival cutoff September 7, 1998		Min f/u 7 mo.
First Survival Update (Submitted w/ NDA*)	January 24, 1999		Min f/u 12 mo.
NDA Submission	September 20, 1999		
Second Survival Update (Submitted w/ Safety Update)	September 15, 1999		

*Submitted with NDA; two additional survival analyses were presented in preNDA meetings.

8.2 Trial Results

8.2.1 Conduct of the Study

- **DSI Audits**

Audits of SO14796 were not conducted.

8.2.2 Enrollment, Disposition, Demographics, Baseline Characteristics

- **Enrollment**

A total of 602 patients were randomized to treatment in 11 countries at 59 sites.

Reviewer Table 21*
Enrollment by Country (SO14796)

Country	# Centers	Randomized to Capecitabine N = 301	Randomized to 5-FU/LV N = 301	# Pts N = 602
Israel	2	3	5	8
Russia	4	35	34	69
France	10	30	28	58
Italy	8	35	38	73
Germany	8	29	26	55
Australia	5	25	26	51
U.K. (incl. Scotland)	13	86	87	173
Belgium	2	18	18	36
Spain	4	20	20	40
Taiwan	2	13	8	21
New Zealand	1	7	11	18
Total	**59**	**301**	**301**	**602**

*Derived from data in Sponsor's listing of investigators in vol. 1, pp. 14-38 and vol. 165, p. 90.

The country with the largest accrual, the U.K. (which included Scotland), entered 29 percent of the patients from 13 centers. The single center with the smallest accrual entered 1 patient (#17395; France); the site with the largest accrual (#17420; London) entered 30 patients (5%). Twenty eight centers accrued $\geq$ 10 patients.

- **Disposition**

The median duration of treatment was 147 days for patients receiving capecitabine and 140 days for patients randomized to 5-FU/LV. Information on disposition is derived from the Study Completion form of the CRF which provided 8 categories for coding reasons for withdrawal. The sponsor's Table 13 combines Violation of Selection Criteria and Other Protocol Violation. Data is collected and presented only up to 48 weeks on treatment (i.e., during the treatment and continuation phases).

Sponsor Table 13 (Abridged)*
Disposition (SO14796)

Reasons for Withdrawal	Capecitabine (N = 301)		5-FU/LV (N = 301)	
	No.	%	No.	%
Insuff. Therapeutic Response (PD)	153	50.8	165	54.8
AE/Intercurrent Illness	40	13.3	32	10.6
Patient Refusal	20	6.6	20	6.6
Death	10	3.3	9	3.0
Violation of Selection Criteria plus Other Protocol Violation	4	1.3	-	-
Admin/Other	9	3.0	6	2.0
Failure to Return (Lost to F/U)	-	-	1	0.3
Subtotal	236	78.4	233	77.4
Randomized but not Rx'd	4	1.3	2	0.7

*Vol. 119, p. 57

- **Demographics**

Sponsor's Table 11 presents demographics of the study population by arm. The majority of patients were male: 57% on capecitabine and 5-FU/LV. The arms were balanced with regard to age (mean of 62 years, median of 64); race (approximately 95% caucasian in both arms); and KPS (median KPS 90% on both arms).

Sponsor Table 11 (Abridged) *
Demographics (SO14796)

	Capecitabine (N = 301)	5-FU/LV (N = 301)
SEX		
N	301	301
Males	172 (57%)	173 (57%)
Females	129 (43%)	128 (43%)
AGE (yr)		
N	301	300
Mean	61.9	62.3
SD	19.5	9.4
Median	64.0	63.5
Range	29 - 84	36 - 86
RACE		
N	301 (94%)	301
Caucasian	283 (<1%)	288 (96%)
Black	2 (0%)	2 (<1%)
Oriental	0 –	2 (<1%)
Hispanic	0 –	0 –
Other	16 (5%)	9 (3%)
Karnofsky PS		
N	297	297
Mean	89.7	89.6
SD	9.7	9.7
Median	90.0	90.0
Range		
Body Surface Area (m^2)		
N	301	301
Mean	1.8	1.8
SD	0.2	0.2
Median	1.8	1.8
Range		

*Vol. 165, p. 34

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- **Baseline Characteristics**

The following table presents baseline characteristics of patients by arm. No significant imbalances are noted.

Reviewer Table 22[1]
Baseline Characteristics (SO14796)

	Capecitabine	5-FU/LV
Interval Between Metastatic Disease & Randomization		
Mean ± SD	101.8 ± 273.3	77.2 ± 122.3
Median	46	44
Range		
Location[2]		
Colon	199 (66.1%)	196 (65.1%)
Rectum	101 (33.6%)	105 (34.9%)
Tumor Differentiation[1]		
Well diff.	40 (13.3%)	40 (13.3)
Mod. diff.	186 (61.8%)	180 (59.8%)
Poorly diff.	51 (16.9%)	48 (16.0%)
Undetermined/unknown	24 (8.0%)	33 (11.0%)
No. of Pts. by No. of Metastatic Sites		
0	2[3]	0
1	102	89
2	76	69
3	58	64
4	34	51
5	15	19
>5	14	9
Most Frequent Sites of Metastases		
Liver		
Multiple	202 (67.1%)	214 (71.1%)
Solitary	28 (9.3%)	24 (8.0%)
None	70 (23.2%)	56 (18.6%)
Unknown	1 (0.3%)	7 (2.3%)
Lymph nodes		
Multiple	65 (21.6%)	68 (22.6%)
Solitary	17 (5.6%)	20 (6.6%)
None	206 (68.4%)	203 (67.4%)
Unknown	13 (4.3%)	10 (3.3%)
Lung		
Multiple	78 (25.9%)	75 (24.9%)
Solitary	11 (3.6%)	14 (4.6%)
None	209 (69.4%)	208 (69.1%)
Unknown	3 (1.0%)	4 (1.3%)
Prior Treatment		
Surgery	265 (88.0%)	268 (89.0%)
XRT	42 (14.0%)	42 (14.0%)
Adjuvant 5-FU	56 (18.6%)	41 (13.6%)

[1]Derived from Sponsor's Tables 19, 20, 21, 22, 23 in vol. 119 pp. 62 - 65.
[2]One patient (#17420/1816) randomized to capecitabine did not have confirmation of cancer.
[3]Two patients randomized to capecitabine (#17420/1823 and #17423/2427) did not have confirmation of metastatic sites.

8.2.3 Efficacy Results

8.2.3.1 Response Rate

The two phase 3 protocols were identical and so protocol SO14796 also specified the IRC measurements as primary for determining RR, response duration and TTP. The FDA asked that the investigator and IRC assessments be reconciled to yield a single efficacy determination also for SO14796. The algorithm described in Section 7.2.3.1was used for reconciling differences. All three determinations of RR for the ITT population, i.e. investigator, IRC and reconciled, are shown in Reviewer Table 23.

Reviewer Table 23:
Response Rate (ITT Population; SO14796)

	Capecitabine (N = 302)		5-FU/LV (N = 303)	
Investigator				
N	297	98%	301	99%
RR	80	27%	54	18%
CR	7	2%	7	23%
PR	73	24%	47	16%
SD	142	47%	157	52%
PD	48	16%	62	20%
Missing postbaseline information	27	9%	28	9%
χ^2	p = 0.013			
IRC				
N	299	99%	301	99%
RR	57	19%	45	15%
CR	1	0.3%	2	0.7%
PR	56	18%	43	14%
SD	171	57%	167	55%
PD	38	13%	51	17%
Missing postbaseline information	33	11%	38	12%
χ^2	p = 0.21			
Sponsor ("reconciled")				
N	301	99.7%	301	99.4%
RR	62	21%	41	14%
(95% CI)		(16.17, 25.61)		(9.96,18.02)
CR	0	0	2	0.7%
PR	62	21%	39	13%
SD	156	52%	156	52%
PD	54	18%	76	25%
Missing post-baseline information[1]	29	10%	28	9%
χ^2	p = 0.027			

*Data derived from Sponsor's Table 25 and 27, vol. 31, p. 64 - 65; Table 3, vol.171, p. 10.
[1]Defined as patients who were withdrawn or died before 42 days; counted as nonresponders.

Reviewer Comment: *Eligibility criteria required at least one bidimensionally measurable lesion. Cross-reference of Listing 2.1 (Patient Listing of Lesion Description – Investigator; vol. 129), 2.5 (Patient Listing of Lesion Description – IRC; vol. 129) and Appendix 9 (List of Violations; vol. 119) indicates that only 1 patient on 5-FU/LV (#17388/5219) and 4 patients on capecitabine (#17406/4009, #17406/4002, #17411/1205, #17430/7708) lacked bidimensionally measurable disease at baseline.*

A random sample of CRFs from responders was reviewed. No disagreements were found with the reconciled assessment as provided in Appendix 1: Listing of Tumor Response by Patient—Reconciled data (vol. 171, pp. 18-28).

The percentage of missing post-baseline information is balanced between the arms (10% in the reconciled assessment) as are the reasons for being missing (see Reviewer Table 24 below).

Reviewer Table 24:
Reasons for Missing Post-Baseline Information (SO14796)

Reason	*Capecitabine*		*5-FU/LV*	
	Sponsor	*FDA*	*Sponsor*	*FDA*
Refused Rx	*6*	*8* *• #17429/1816 refused all rx* *• #17401/4103 refused all rx* *(Counted by sponsor as violations)*	*6*	*6*
Death	*8*	*8*	*8*	*8*
AE or Intercurrent Ill.	*11*	*11*	*14*	*14*
Insufficient Rx	*0*	*0*	*0*	*0*
Violation	*3*	*1* *(2 pts moved to "refused rx.")*	*0*	*0*
Admin/Other	*1*	*1* *• #17402/4301 rec'd 1d of rx*	*0*	*0*
?	*0*	*0*	*0*	*0*
TOTAL	*29 (10%)*	*29 (10%)*	*28 (10%)*	*28 (9%)*

- **Concomitant "Anticancer" Treatment**

The protocol section, "Concomitant Medication and Treatment," did not explicitly prohibit other anticancer therapy. The CRF required listing of all concomitant medications. The following table presents treatment with other therapy that could be considered "anticancer," including radiotherapy (XRT), during study. Not included in the table are treatments that were started after the last date of study drug or within the last week of study drug.

Reviewer Table 25*
Patients who received Concomitant Treatment with Potential Anticancer Agents (SO14796)

	Capecitabine Pt #: Measurable Disease	Best Response	5-FU/LV Pt #: Measurable Disease	Best Response
Progestogens	9		5	
Immunostimulants			1 #17408/4802: liver. Jomol (bacterial cell wall extract) & Eunova (vitamins)	SD
Folinic Acid			1 #17413/1115: liver	PR
Unknown Rx Given	3 #17388/5218: liver, lung #17408/4803: liver #17423/2408: "pelvic"	 No assessment No assessment SD		
XRT	1 #17391/5508: liver. Dates of XRT unk	SD	1 #17383/3515: liver. XRT given to sacrum	PD

Data derived from June 30, 2000 correspondence; list 2.1 and 2.2, vol. 129; reconciled response data, vol. 171

Reviewer Comment: *Treatments administered do not appear to be confounding. No approved agents for the treatment of colorectal cancer were co-administered. The exception might be co-administration of folinic acid; however, the patient was already receiving leucovorin. The two patients who received XRT on study were not counted as responders.*

- **Exploratory Analysis: Response Rates in Subgroups**

The sponsor conducted exploratory analyses of response rate in a variety of subgroups: center size (≤ 10 or > 10 patients), number of metastatic sites at baseline (1 vs. 2 vs. 3 vs. 4 vs. >4), age (≤ 60 or > 60), predominant site of metastasis (liver vs. lung vs. soft tissue vs. other visceral), colon vs. rectal primary, race (caucasian vs. back vs. other) and prior adjuvant chemotherapy. RR with capecitabine trended higher in most subgroups, including in the category of race designated "other."

8.2.3 Response Duration

For those who had responded to the treatment regimens, the median duration for capecitabine-treated patients was 348 days. The median duration for 5-FU/LV-treated patients was 327 days. No comparison of median durations between the two treatment arms should be made because the subgroups are selected and nonrandomized.

8.2.4 TTP

Time to progressive disease was measured from the date of randomization until the date of documented disease progression or death. The analysis was performed on the "reconciled" dataset (see Section 7.2.3.1 for methodology of reconciliation). The results are presented in Reviewer Table 26. There was no statistically significant difference between the treatment arms (p = 0.68, log-rank test).

Reviewer Table 26: TTP (S014796)

	Xeloda	5FU/LV
TTP		
median ("reconciled")	4.7 mo.* 137 days	4.4 mo. 131 days
95% CI	(128, 165)	(102, 156)
HR	0.97	
95% CI	(0.82, 1.14)	

*Months calculated by days divided by 30.

Reviewer Comment: *The sponsor states that the two treatment arms are equivalent based on the upper and lower bounds of the 95% CI of the HR. However, as discussed elsewhere in this review (assessment of survival and in Appendix II: FDA Non-inferiority Analyses), a claim for non-inferiority requires demonstration that a clinically meaningful fraction of the treatment effect of 5-FU/LV vs. 5-FU is preserved.*

8.2.5 Survival

Overall survival was measured from the date of randomization until the date of death. The protocol-specified test for non-inferiority in survival was defined quantitatively as the upper bound of the 95% CI of the HR of capecitabine to 5-FU/LV. If the upper limit did not exceed 1.25 while testing at the 2.5% α-level, non-inferiority could be concluded. The results for overall survival based the January 24, 1999 and the May 15, 2000 cutoff are shown in Reviewer Table 27. Overall survival based on the ITT population is not statistically significantly different between the treatment arms (p=0.84, log-rank test).

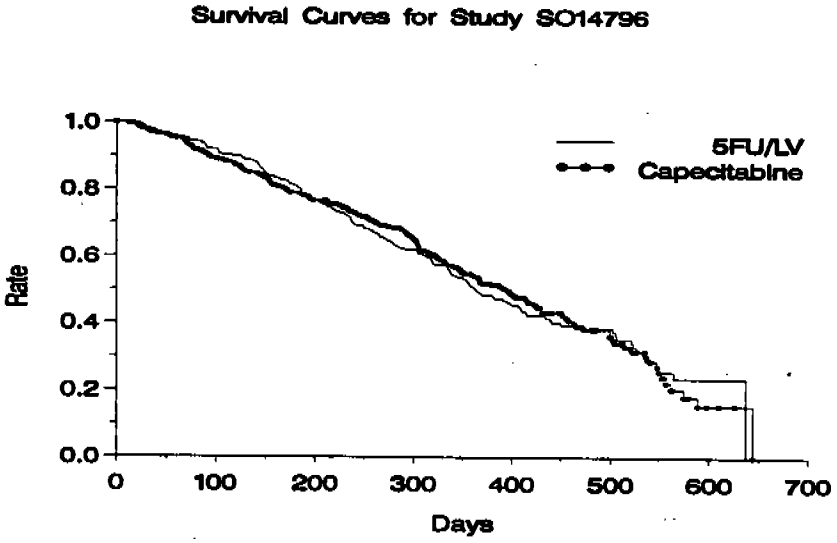
Reviewer Table 27: Overall Survival in the ITT population (SO14796)

	Xeloda N = 301	5FU/LV N = 301
[redacted]		
Survival		
• **Median**	13.5 mo.*	12.6 mo.
	404 days	379 days
95% CI	(367, 452)	(338, 434)
# Events	192 (63.8%)	194 (64.5%)
• **HR** (Xeloda:5-FU/LV)	0.98	
95% CI	(0.80; 1.20)	
[redacted]		
Survival		
• **Median**	13.5 mo.	12.3 mo.
	404 days	369 days
95% CI	(367, 452)	(338, 430)
# Events	261 (87%)	272 (90%)
• **HR** (Xeloda:5-FU/LV)	0.92	
95% CI	(0.78, 1.09)	

* Months calculated by days divided by 30.

The Kaplan-Meier curves based on the January 1999 cutoff are presented in Reviewer Figure 3.

Reviewer Figure 3



- **Protocol-Defined Exploratory Analysis: Survival in the "Standard Population"**

The sponsor prospectively defined an evaluable patient population ("standard" -- see Section 7.1.8 of the protocol review) for exploratory analyses. Of the 602 patients randomized, 36 (12%) on capecitabine and 28 (9%) on 5-FU/LV were excluded from the standard population leaving a total of 538 patients. Reasons for exclusion are displayed in Reviewer Table 28.

Reviewer Table 28*:
Summary of Reasons for Exclusion from Standard Population (SO14796)

Reason for Exclusion	Capecitabine (N = 265)	5-FU/LV (N = 273)
Did not receive treatment	4	2
Rcd < 6 wks of Rx w/o PD or death	14	15
Rcd < 50% of rx in first 6 wks	5	1
Inadequate tumor assessment	13	10
Major protocol violation	-	-
Total	36	28

*Data derived from Sponsor Table 17, vol. 119, p.59

Analysis in the standard population is of interest since the ICH E9 guidance raised the issue that an ITT analysis is not conservative when testing for non-inferiority. There appears to be comparable dropout per arm. The following analysis provided by the sponsor (not confirmed by the FDA) is exploratory. The log rank test p value is 0.68.

Reviewer Table 29:
Overall Survival in the Standard Population (S014696)

	Xeloda (N = 265)	5FU/LV (N = 273)
Database Closure: [redacted] 1999		
Survival		
• **Median**	13.7 mo.* 411 days	13.0 mo. 391 days
95% CI	(373; 458)	((355; 450)
# Events	163 (61.5%)	174 (63.7%))
• **HR** (Xeloda:5-FU/LV) 95% CI	0.96 (0.77; 1.19)	

Months calculated by days divided by 30.

Reviewer Comment: *Results of analyses on the standard population (upper bounds of the 95% CI for the HR of 1.19) and for the ITT population (1.20) are similar.*

- **Protocol-Defined Exploratory Analysis: Cox Regression for Prognostic Factors, Including Age and Gender**

The protocol had specified a Cox regression analyses on TTP, stratifying for the following covariates: country, large (>5 patients) vs. small centers, gender, differentiation, liver metastases, predominant site of disease at baseline, number of metastatic sites at baseline, location in the colon vs. rectum, KPS, age, race, number of prior regimens and prior adjuvant therapy. These same covariates were used in a Cox regression analysis on survival. A multivariate analysis was performed including all covariates seen as significant at the 15% level in the univariate analysis. The least significant factor was excluded from the model until all factors were significant at 5% (final multivariate model). Five factors were retained in the model. In the order of most significant to least, they are: number of metastatic sites, KPS 80%, KPS 70%, primary site in the liver, and country: France. Age and gender were not significant factors.